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Pharmacodynamics and Pharmacokinetics of Methadone during the Perioperative Period

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The duration of postoperative pain relief was assessed in 23 general surgical or orthopedic patients administered 20 mg methadone as an iv bolus following induction of anesthesia. Nine patients (39%) were pain-free and required no additional analgesia for the control of their postoperative pain (Group 1). Eight patients (35%) required additional narcotic injections (Group 3) but the duration of adequate analgesia was 18.4 ± 6.6 h (mean ± SD). The remaining six patients (26%) requested non-narcotic analgesia (Group 2) for the control of their postoperative pain and the mean (±SD) time to the first supplementary dose was 26.5 ± 4.8 h in these patients. The overall median duration of analgesia resulting from the 20 mg methadone was 27 h (n = 23). The mean (±SD) minimum effective analgetic blood methadone concentration was 30 ± 11 ng/ml for the narcotic-supplemented group, and 33 ± 12 ng/ml for the non-narcotic-supplemented group. The results obtained suggest there is a relationship between the blood methadone concentration and the control of postoperative pain.

Patients were sedated in the immediate postoperative period, but their respiratory rate was not depressed significantly (*i.e.*, rate <10 breaths/min). In no case was it necessary to antagonize methadone with naloxone to initiate spontaneous respiration at the termination of the anesthetic. Nausea or vomiting occurred in 11 patients, but they responded to conventional antiemetic therapy.

Sequential blood samples were collected in 19 of the patients for estimation of methadone pharmacokinetics. The mean (±SD) methadone clearance was 178 ± 100 ml/min (*i.e.*, 2.7 ± 1.7 ml · min^{-1} · kg^{-1}), while the terminal half-life was 35 ± 22 h. These results suggest that methadone analgesia is related to the blood concentration of the drug and prolonged postoperative analgesia was consistent with the long half-life of the drug. There was a positive correlation between the methadone initial volume of distribution (76 ± 49 l) and volume of distribution at steady-state (410 ± 156 l) and body weight. Although there was a positive correlation between age of the patient and terminal half-life, no relationship existed between methadone clearance and age of the patient. Surprisingly, there was a highly significant negative correlation between methadone clearance and the minimum effective analgetic blood methadone concentration. The variables of duration of analgesia and minimum effective analgetic blood methadone concentration were subjected to multivariable regression analysis. The aim of this analysis was to provide equations to predict the value of these variables prior to surgery. The patient variables which had most influence included age, weight and the Eysenck Personality Inventory dimensions of neuroticism (N score), extroversion (E score), and social conformity (L score).

The authors conclude that methadone has the desirable pharmacokinetic (such as a long half-life and low clearance) and pharmacodynamic properties such that a single dose of 20 mg can result in prolonged postoperative analgesia. (Key words: Analgesics: methadone. Pain: postoperative. Pharmacodynamics: methadone. Pharmacokinetics: methadone.)

POSTOPERATIVE ANALGESIA is often inadequate, despite recent advances in knowledge of narcotic pharmacokinetics and description of precise sites of narcotic action in the brain and spinal cord. Repeated intramuscular injection of short (3–4 h) half-life narcotics is the traditional method of providing such analgesia. However, resulting fluctuations in blood narcotic concentration[1] produces a clinical response which can range from ineffective analgesia to toxicity and unwanted side effects with relatively brief periods of adequate analgesia in between these extremes.

Constant intravenous infusion techniques may improve management of postoperative pain[2] by significantly reducing the fluctuations in blood narcotic concentration. Such techniques are being developed "as a means of remedying the clinically significant problem of ineffective and inefficient use of narcotic analgesics for the relief of pain."[3] Both constant[2] and *demand*[4] narcotic infusion techniques require relatively expensive infusion pumps, with adequate *fail-safe* mechanisms, which generally include intensive nursing surveillance.

Recently, alternative experimental methods of narcotic administration have included intrathecal and epidural routes because of the identification of narcotic receptors in the spinal cord. These routes are technically difficult and not without significant potential adverse effects such as delayed respiratory depression and urinary retention. Problems associated with use of any nar-

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cotic drug in the control of postoperative pain have been clearly defined by Hug.[3] They are related to unwanted effects of these agents: respiratory depression, cardiovascular instability, drowsiness, nausea, and vomiting.

An alternative to the above methods is the use of a narcotic with a long half-life which may provide stable blood concentrations after a single intravenous dose, without the fluctuations associated with repeated im injection of the high clearance narcotics (*e.g.*, morphine and pethidine [meperidine]). It could be predicted that the use of a long half-life narcotic (*e.g.*, methadone) may provide prolonged and constant analgesia.

In this study, an old drug, methadone, was used by an established route of administration—the intravenous bolus. Blood concentrations of methadone were measured after surgery and duration of analgesia was assessed, together with the requirement for supplementary narcotic and non-narcotic drugs. Further, this study examines the relationship between methadone pharmacodynamics and pharmacokinetics relating to the treatment of postoperative pain.

Patients and Methods

Patients

Institutional approval (by the Clinical Investigation Committee and the Drug and Therapeutic Advisory Committee) was obtained for the study, and each patient gave informed consent. Twenty-three healthy adult patients (ASA status I or II) with no history of narcotic abuse were studied during and after elective surgery (table 1). No narcotic had been used in the preceding 24 h. Patients were not selected in any way apart from being the first patient on the anesthesiologist's list on the study day to provide a maximum time of close observation in the postoperative period.

Anesthesia

Premedication consisted of 0.1 mg/kg droperidol, im, one hour prior to induction at 0800 h. After appropriate local anesthesia (procaine), a forearm vein was cannulated for fluid and drug administration, and a subclavian vein catheter was placed via the contralateral antecubital fossae for serial blood sampling (Bardi®-intracath 18-14 fitted with a double three-way Cobe® stopcock). Anesthesia was induced with thiopentone (4–5 mg/kg), and pancuronium (0.1 mg/kg) facilitated endotracheal intubation and intermittent positive pressure ventilation with nitrous oxide (70%) and oxygen (30%). Enflurane was added (0.5–1%) if the depth of anesthesia was considered inadequate to prevent awareness. Non-invasive monitoring (ECG, BP, pulse, VT) was continued throughout the anesthetic. After intubation, when cardiovascular stability was attained (5–10 min), 20 mg methadone was administered as an intravenous bolus (over 1 min) in the contralateral arm to the blood sampling catheter. This time period was chosen to minimize the respiratory depressant effects of intravenous narcotics as the patient was paralyzed and ventilated. Neuromuscular blockade was antagonized with neostigmine/atropine at the termination of the surgical procedure. All operations were in excess of one hour in duration.

Postoperative Management

Patients had been informed at the pre-anesthetic visit on the day before surgery that additional analgesia would be available postoperatively when it was required. They also were informed that they would have the free choice of intramuscular (narcotic) or oral (non-narcotic) supplements. They were seen at regular intervals by the nursing staff, and at least hourly by one of the investigators during blood sampling. A nurse call-button was in immediate reach. The pain level was recorded essentially as described by Stapleton *et al.*[2] during each hourly visit by one of the principal investigators. The modification to the method involved the patients' choice of narcotic or non-narcotic medication when pain returned. Nursing staff had been informed of the study and were instructed not to give medications *routinely* or *to settle* the patient. An additional blood sample was collected at the time the patient considered the pain to be severe enough to require additional analgesia. The blood concentration at this time was termed the minimum effective analgetic concentration. The duration of analgesia was defined as the latency between the time of methadone administration and the time at which additional analgesia was administered. When obtaining consent, care was taken not to imply that methadone would have an unexpectedly long duration of action. A single dose of methadone (20 mg) was administered in this study since no information was available on methadone pharmacodynamics in postoperative patients at this dose.

The amount of postoperative narcotic administered to Group 3 (table 1) patients were expressed as mg morphine equivalents, assuming that 10 mg morphine was equivalent in terms of potency (*i.e.*, intensity and not including duration of action) to 75 mg pethidine, 20 mg papaveretum, and 10 mg methadone.[5]

In a subsection of this study, 12 patients completed the Eysenck Personality Inventory[6] (EPI) form B which yields scores on the dimensions of neuroticism (N), ex-

TABLE 1. Methadone Study Patients

Patients	Type of Operation	Age (years)	Sex	Weight (kg)	Time to First Supplementary Analgesia (hours)	Amount of Narcotic (mg morphine equivalent)			Number of Injections			Minimum Effective Analgesic Concentration (ng/ml)
						0–48 h	>48 h	Total*	0–24 h	24–48 h	>48 h	
Group 1 No supplementary analgesia												
1	Anterior spinal fusion	48	F	59.6	P†	0	0	20	0	0	0	P
2	Anterior spinal fusion	40	M	70	P	0	0	20	0	0	0	P
3	Anterior spinal fusion	44	F	54	P	0	0	20	0	0	0	P
4	Bilateral varicose veins	41	M	74.7	P	0	0	20	0	0	0	P
5	Cholecystectomy	59	M	59.8	P	0	0	20	0	0	0	P
6	Cholecystectomy	52	F	67.5	P	0	0	20	0	0	0	P
7	Cholecystectomy	39	F	74.9	P	0	0	20	0	0	0	P
8	Lower abdominal	50	M	86.5	P	0	0	20	0	0	0	P
9	Laminectomy	44	F	58	P	0	0	20	0	0	0	P
Group 2 Non-narcotic postoperative analgesia												
10	Cholecystectomy	69	F	58.5	22	0	0	20	0	0	0	30
11	Cholecystectomy	67	F	47.2	35	0	0	20	0	0	0	33
12	Gastrectomy	57	F	48	24	0	0	20	0	0	0	54
13	Hiatus hernia (abdominal)	49	M	85	28	0	0	20	0	0	0	35
14	Lower abdominal	57	M	92.5	27	0	0	20	0	0	0	29
15	Bilateral varicose veins	58	F	64.3	23	0	0	20	0	0	0	18
Mean ± SD					26.5 ± 4.8							33 ± 12
Median value					26							31.5
Group 3 Narcotic postoperative analgesia												
16	Anterior spinal fusion	29	M	60.5	15.5	20	0	40	1	1	0	ND
17	Anterior spinal fusion	43	F	70	9	30	80	130	2	1	8	ND
18	Anterior spinal fusion	45	M	74	13.5	40	0	60	1	2	0	19
19	Anterior spinal fusion	54	M	76	25	60	20	100	4	2	2	ND
20	Anterior spinal fusion	49	M	70	12	60	120	200	1	3	8	34
21	Anterior spinal fusion	41	F	76.6	24	45	15	80	0	3	1	46
22	Anterior spinal fusion	44	F	58	24	10	0	30	0	1	0	31
23	Lower abdominal	56	M	69.7	24.2	60	0	80	0	5	4	19
Mean ± SD					18.4 ± 6.6	40.6 ± 19.4	29.4 ± 45.5	90 ± 55				30 ± 11
Median value					20	42.5	7.5	80	1	2	1	31
Median value (Groups 1, 2, and 3 combined)					27							

* Total narcotic includes 20 mg intraoperative methadone.
ND represents not determined.

† P = prolonged analgesia

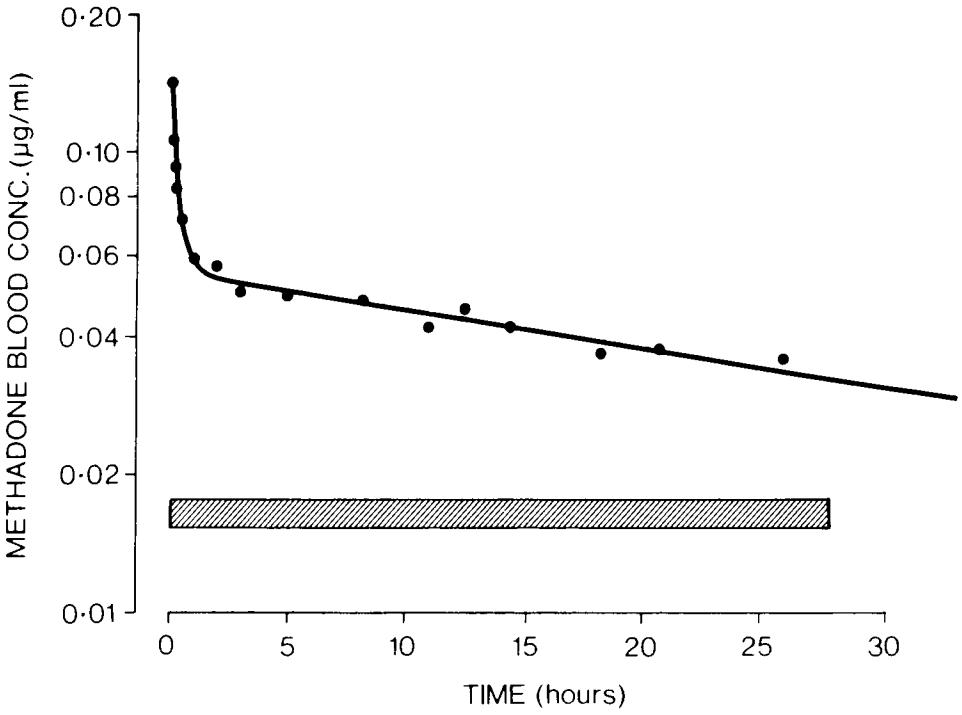

FIG. 1. Blood methadone concentration (μg/ml) as a function of time (hours) in a patient undergoing repair of a hiatus hernia. The 49-year-old man was administered 20 mg of methadone as an iv bolus following induction of anesthesia. The points (●) represent the measured blood methadone concentrations, while the curve represents the computer-generated line of best fit of a biexponential equation to the data. The shaded area represents the time period that the patient was continuously free of pain (*i.e.*, 28 h). This patient had a methadone clearance of 113 ml/min and a terminal half-life of 36.5 h.

troversion (E), and social conformity (L) the night before surgery.

Blood Sampling and Methadone Assay Procedure

Blood samples were collected from 19 of the 23 patients (patients not included in the pharmacokinetic study were numbers 1, 16, 17, and 19 in table 1 because blood could not be aspirated from the blood sampling catheter during the study) for pharmacokinetic studies at the following times following a 20-mg iv bolus methadone dose: 0, 2, 5, 10, 15, and 30 min; 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 20, 24, 28, 32, and 36 h, and in some cases, 48 h. The blood samples (1 ml) were added to glass tubes containing heparin (25 IU) and internal standard (bupivacaine 0.5 μg). Samples were frozen (−15° C) for a maximum of 7 days until assayed. Unpublished studies in this laboratory have shown that methadone samples are stable for at least 1 month in these storage conditions. The amount of methadone in each blood sample was measured using a Hewlett-Packard® 5710 or 5730 gas chromatograph, equipped with dual nitrogen-phosphorus detectors.

The extraction procedure used prior to gas chromatographic analysis was identical to that described previously.[7] Briefly, the chromatography conditions were as follows: a glass column (2-m × 2-mm, id) was packed with 3% OV-25 on Gas Chrom Q (100–120 mesh) (Applied Science Labs). The oven, injector port, and detector temperatures were 235° C, 250° C, and 300° C, respectively, with a carrier gas (pure nitrogen) flow of 30 ml/min. The nitrogen-phosphorus detectors were optimized according to the manufacturers recommendation using hydrogen and air flows of 3 ml/min and 50 ml/min, respectively. Under these conditions, the retention times for methadone and bupivacaine were 2.0 and 3.5 min, respectively. A 3% OV-17 column on Gas Chrom Q operated with an oven temperature of 250° C gives essentially identical chromatography.

Standard curves were always linear and passed through the origin. The lower limit of sensitivity was 10 ng/ml of whole blood, and the reproducibility of replicate samples was 3–5% at the lower end and 2–3% at the upper end of the standard curve.

Calculation of Pharmacokinetic Parameters

Data from the blood methadone concentration *vs.* time graphs were fitted to a biexponential equation using an iterative nonlinear least-squares technique with a digital computer. Pharmacokinetic parameters were calculated from the equation coefficients and exponents by the model-independent techniques described by Wagner.[8]

Statistical Analysis of the Data

The Statistical Package for the Social Sciences (SPSS)[9] was used for all statistical analysis (release 8.0, December 1979) of the data on a digital computer (DEC System 10, Digital Equipment Corporation). The subpro-

TABLE 2. Pharmacokinetics and Pharmacodynamics of Methadone during the Perioperative Period

Variable		Mean	SD	Median	Minimum	Maximum
Clearance	(ml/min)	178	100	177	39	407
	($ml \cdot min^{-1} \cdot kg^{-1}$)	2.7	1.7	2.5	0.7	7.5
V_C*	(l)	76	49	65	10	197
	(l/kg)	1.1	0.7	0.9	0.1	2.6
V_{DSS}†	(l)	410	156	387	136	660
	(l/kg)	6.1	2.4	6.1	1.8	12.2
$t_{1/2\alpha}$‡	(min)	6.1	5.7	4.2	1	24
$t_{1/2\beta}$§	(h)	35	22	27	9	87
Duration of analgesia¶		21.4	7.0	27	9	P**

* Initial volume of distribution.
† Volume of distribution as steady-state.
‡ Distribution (alpha) half-life.
§ Elimination (beta) half-life.
¶ Duration of analgesia is expressed in hours. The figures quoted for the mean ± SD are derived from the data excluding patients who had no supplementary analgesia while the median, minimum, and maximum figures are derived from all patients.
** P represents prolonged analgesia, *i.e.*, the patients required no supplementary analgesia (either narcotic or non-narcotic) in the postoperative period. Therefore, a duration of analgesia and a minimum effective blood methadone concentration could not be calculated for these patients.

Pharmacokinetic variables were calculated by fitting the data to a biexponential equation of the form: $C_b = A \exp^{-\alpha t} + B \exp^{-\beta t}$, where C_b represents the blood methadone concentration (ng/ml) at time t (min). The mean values of the constants from the 19 patients were: A = 403 ng/ml, B = 55 ng/mg, $\alpha = 0.23\ min^{-1}$, and $\beta = 4.64 \times 10^{-4}\ min^{-1}$.

grams used were: CONDESCRIPTIVE (descriptive statistics) T-TEST (unpaired Student's *t* test), SCATTERGRAM (produces as two-dimensional plot with correlation analysis), and REGRESSION (multivariable regression). A level of significance of $P < 0.05$ was required to reject the null hypothesis.

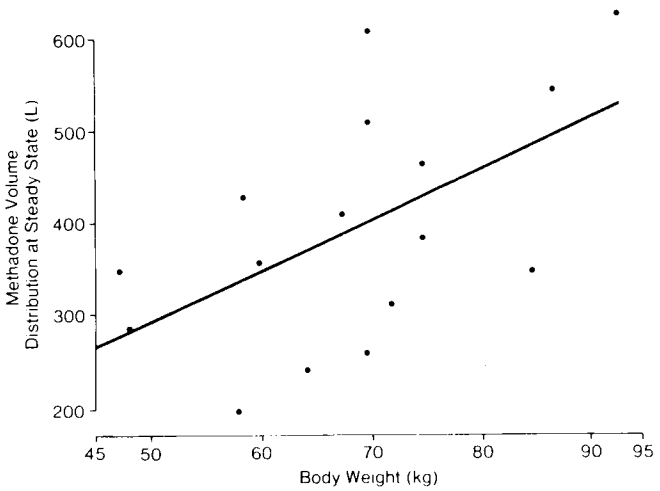

FIG. 2. Correlation of methadone volume of distribution at steady-state (l) with patients' body weight. The r value in all graphs represents the Pearson product-moment correlation coefficient, while the *P* value represents the level of significance of the r value. $P < 0.025$. r = 0.56.

Results

Patient characteristics, operation performed, and results of the measurements of minimum effective blood concentrations of methadone and analgetic effects are summarized in table 1, grouped according to postoperative analgetic requirement. In no patient was it necessary to antagonize the methadone with naloxone to initiate spontaneous respiration.

GROUP 1 (NINE PATIENTS)

Patients were pain-free and did not request any postoperative analgesia in the 72 h of observation. They had surgery which could be expected to produce significant postoperative pain.

GROUP 2 (SIX PATIENTS)

These patients requested oral medication (aspirin/paracetamol) for postoperative pain. They were aware that they were able to request a pain-killing injection if the oral medication was not sufficient to ensure their comfort. The median duration of methadone analgesia in this group was 26 h (range 22–35 h) and the patients were pain-free during this period. Blood was collected at the time of request for supplementary analgesia (table 1), and the minimum effective analgetic blood methadone concentration at this time was (median value) 31.5 ng/ml (range 18–54 ng/ml).

GROUP 3 (EIGHT PATIENTS)

These patients received supplementary intramuscular narcotic (either morphine or pethidine) to control the postoperative pain. Median time from methadone administration to supplementary injection was 20 h (range 9–25 h), and the patients were pain-free during this time period. Median methadone blood concentration at the time of request for analgesia was 31 ng/ml (range 19–46 ng/ml). This group received a mean of 40.6 mg (not including 20 mg of methadone intraoperatively) morphine equivalent in the 48 h following anesthesia (table 1).

An example of the blood methadone concentration (μg/ml) *vs.* time (h) curve for one of these patients administered 20 mg methadone as an iv bolus, together with the duration of continuous analgesia is provided in figure 1. This patient (#13, table 1) was a 49-year-old man who required repair of a hiatus hernia (abdominal approach). It is apparent that the blood methadone concentration rapidly falls immediately following iv administration (*i.e.*, has a rapid distribution phase). Then, the blood methadone concentration slowly falls during the elimination phase and does not show the rapid oscillations in blood narcotic concentration asso-

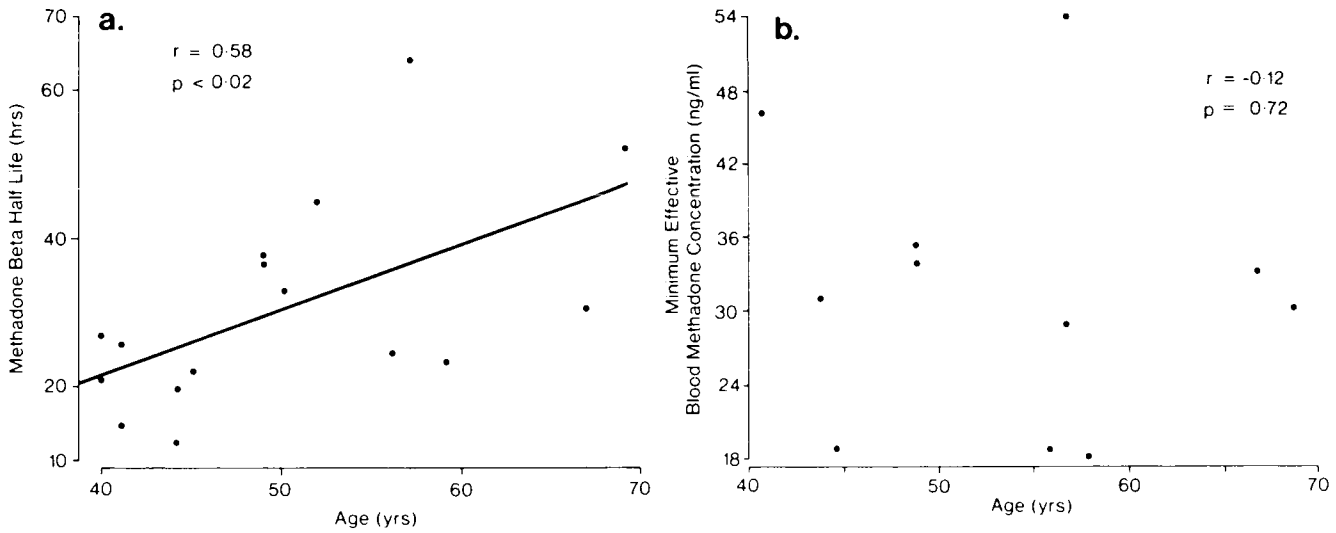

FIG. 3. Correlation of (*A*) methadone beta half-life and (*B*) minimum effective analgetic blood methadone concentration with patient age. The r value represents the Pearson product-moment correlation coefficient, while the *P* value represents the level of significance of the correlation analysis.

ciated with repeated im injections. The duration of continuous analgesia was 28 h in this patient.

The blood concentration-time data from this patient, as well as similar data from all other patients could adequately be fitted to a biexponential equation. Table 2 provides the pharmacokinetic parameters (calculated by model independent techniques)[8] of methadone in the perioperative period. Methadone has a rapid distribution half-life of 6.1 ± 5.7 min (mean ± SD), and a large volume of distribution at steady-state (410 ± 156 l). The mean methadone clearance was 178 ml/min, while the terminal half-life was 35 ± 22 h.

There was a positive correlation between the volume of distribution at steady-state ($r = 0.56$, $P < 0.025$) and patient body weight following the administration of 20 mg methadone to all patients (fig. 2). Similarly, the initial volume of distribution correlated with the patient's body weight ($r = 0.57$, $P < 0.02$). Although there was a positive correlation between patient age and terminal half-life (fig. 3*A*), no relationship existed between methadone clearance and patient age or the volume of distribution at steady-state and patient age. Similarly, no correlation ($r = -0.12$, $P = 0.72$) was found between the minimum effective analgetic blood methadone concentration and patient age (fig. 3*B*).

There was a highly significant negative correlation (fig. 4) between methadone clearance and the minimum effective analgetic blood methadone concentration ($r = -0.83$, $P < 0.002$). It is apparent that while there is statistically significant correlation between some of the variables quoted, the strength of the correlation is not always sufficiently large to allow accurate prediction of various parameters from the data. The data were therefore subjected to multivariable regression analysis in an attempt to improve the strength of correlation.

Table 3 shows the results of multivariable regression analysis for the estimation of duration of analgesia (dependent variable) resulting from a 20 mg iv dose of methadone. The variables of age, neuroticism score (N), extroversion score (E), and social conformity score (L) had the most influence on the dependent variable and were individually added during regression analysis. A refined regression equation was calculated together with statistical analysis after each variable was added (table 3). The coefficients, either positive or negative,

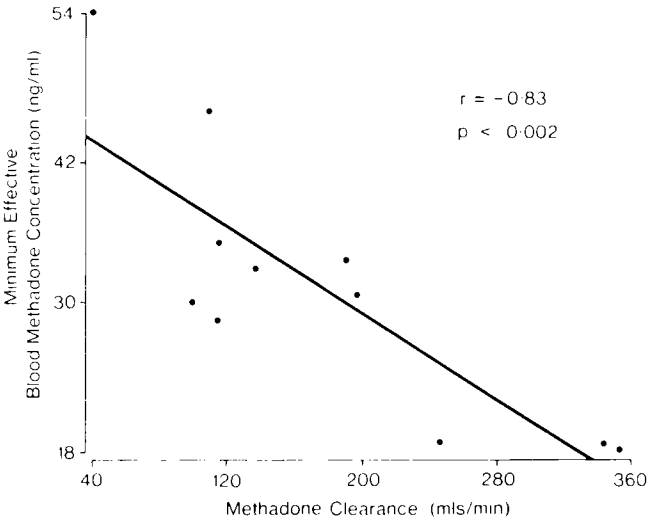

FIG. 4. Correlation of minimum effective analgetic blood methadone concentration (ng/ml) with methadone clearance (ml/min). $r = -0.83$. $P < 0.002$.

TABLE 3. Multivariable Regression Analysis for the Dependent Variable of Duration of Analgesia (in Hours)*

Equation	1	2	3	4
Constant	10.2	−6.06	10.2	4.75
N†	1.11	1.65	2.29	2.05
L‡	——	4.05	8.97	8.2
Age§	——	——	0.63	0.55
E¶	——	——	——	0.36
r**	0.628	0.922	0.991	0.999
r^2	0.394	0.849	0.982	0.999
Change in r^2	0.394	0.455	0.133	0.017
Standard error††	6.5	3.7	1.56	0.5

* In this multivariable regression analysis, the variables are included into the regression equation in a stepwise manner.

† N represents the Eysenck Personality Inventory Neuroticism score.

‡ L represents the Eysenck Personality Inventory Social Conformity score.

§ Age represents patient age.

¶ E represents the Eysenck Personality Inventory Extroversion score.

** Correlation coefficient.

†† Standard error of the estimate: The value assigned to the standard error in any of the equations indicates that 68% of individuals will fall in the range of ± 1 SE value from the duration of analgesia calculated from that equation in absolute units. (*i.e.*, hours in this case). Similarly, 95% of individuals will fall in the range of ± 1.96 times the SE value.

of each variable for the four equations are provided in table 3. The most complex equation (*i.e.*, equation 4) is

$$\text{Duration of Analgesia (h)} = 4.75 + 2.05N + 8.2L - 0.55\ \text{Age} + 0.36E.$$

The correlation coefficient (r) and r^2 value for equation 4 was 0.999. The r^2 value of 0.999 indicates that 99.9% of the variation in the duration of analgesia is explained by N, L, age, and E operating jointly.[9] The "Change in r^2" value of table 3 indicates the extent to which the inclusion of each extra variable improves the overall variation of the duration of analgesia. For example, the inclusion of the L variable in equation 2 improves the variation in the Duration of Analgesia calculated by equation 2 by 45.5% to a total of 84.9%, and the inclusion of the variable E in equation 4 improves the variation by only 1.7%. However, as stated previously, 99.9% of the variation in the duration of analgesia is accounted for by the variables in equation 4. The standard error of 0.5 in equation 4 (table 3) indicates that 68% of patients will have values in the range of ±1 SE unit (*i.e.*, 0.5 h in this case) from the duration of analgesia calculated using that equation.

TABLE 4. Multivariable Regression Analysis of the Dependent Variable of Minimum Effective Blood Methadone Concentration (ng/ml)*

Equation	1	2	3	4
Constant	50.0	80.4	70.0	72.1
L†	−5.29	−7.16	−7.08	−7.3
Weight‡	——	−0.4	−0.41	−0.43
E§	——	——	0.75	0.85
N¶	——	——	——	−0.16
r**	0.718	0.969	0.999	1.000
r^2	0.516	0.939	0.997	1.000
Change in r^2	0.516	0.423	0.058	0.003
Standard error††	7.8	3.2	0.8	0.01

* In this multivariable regression analysis, the variables are included into the regression equation in a stepwise manner.

† L represents Eysenck Personality Inventory Social Conformity score.

‡ Represents patient weight.

§ E represents Eysenck Personality Inventory Extroversion Score.

¶ N represents Eysenck Personality Inventory Neuroticism Score.

** Correlation coefficient.

†† Standard error of the Estimate (see Table 3 for explanation).

A similar multivariable regression analysis was performed with the minimum effective analgetic blood methadone concentration as the dependent variable (table 4). The variables included in a stepwise manner for the regression equation were weight, N, E, and L. In this case, equation 3 has an r^2 value of 0.997, with a standard error of the estimate of 0.8 ng/ml.

$$\text{Minimum Effective Blood Methadone Concentration (ng/ml)} = 70 - 7.08L - 0.41\ \text{Weight} + 0.75E.$$

The side effects encountered in the present study were similar to those reported for the other narcotic agonists. Patients were sedated but their respiratory rate was not significantly depressed (*i.e.*, rate <10 breaths/min) in the immediate postoperative period. Nausea or vomiting occurred in 11 patients, and they responded well to one or two injections of conventional antiemetic therapy.

Discussion

Relief of postoperative pain is still a subject of significant investigation because present methods may be inadequate.[10] Systemic (usually im) narcotic analgesia provides the most common method, possibly because of its long tradition. Hug[3] has defined certain problems associated with narcotic use and which may contribute to their ineffective use. Ventilatory depression is a dose-related response to narcotic administration,[11] and efforts to minimize such depression might lead to prescription of suboptimal narcotic dosage. There is only anecdotal evidence that postoperative pain itself is an antagonist to respiratory depression.[12] Interaction between narcotics and central depressants may increase the degree of respiratory depression.

Methadone is known to have a half-life ranging from 25[13] to 52 h[14] in narcotic-dependent patients. It is this characteristic together with its high oral bioavailability

which enables methadone to be used by single daily doses to prevent withdrawal symptoms in maintenance programs. However, it has a reputation for providing only short duration analgesia.[15,16,§] The evidence presented here suggests that methadone analgesia is related to the blood concentration of the drug, and prolonged postoperative analgesia was consistent with the long half-life of the drug (table 2).

In the present study, intravenous administration of a single dose of 20 mg methadone during surgery had significant effects on postoperative analgetic drug requirements. Thirty-nine per cent (nine out of 23) of patients required no postoperative narcotic (Group 1, table 1) while 35% of patients required additional narcotic injections (Group 3); the remaining 26% of patients received non-narcotic postoperative analgesia (Group 2, table 1). The duration of analgesia and the minimum effective analgesic methadone concentration could not be calculated for Group 1 patients and is represented in table 1 as P (representing prolonged analgesia). The median duration of analgesia was 26 h (mean value, 26.5 h) for Group 2 (non-narcotic) patients and 20 h (mean value, 18.4 h) for Group 3 (narcotic) patients. The median duration of methadone analgesia from all the 23 patients was 27 h (table 1). Therefore, the duration of analgesia is similar to the mean terminal half-life of 35 h in these postoperative patients (table 2). Group 1 patients (table 1) reported that they were pain-free for the entire observation period, while Group 2 and 3 patients were pain-free until they requested analgesia at the times noted in table 1. The quality of pain relief met with widespread patient acceptance, particularly in those patients with a prior surgical procedure for comparison. Subjectively, all patients noted when asked on the fourth or fifth postoperative day that the pain relief was much greater than expected.

It is suggested that the prolonged analgesia is related to the slowly decreasing blood methadone concentration in the elimination phase (which commences at approximately 50 min in fig. 1). Figure 1 also shows that there is a pronounced distribution phase (mean $t_{1/2\alpha}$ of 6.1 min, table 2) following iv bolus administration of methadone. The results obtained in this study are at variance with literature references of 3–4 h for the duration of analgesia resulting from parenteral methadone administration.[15,16] It is suggested that the reason for this discrepancy lies in the dose of methadone administered. Many references[5,17,18] state that methadone is equipotent (in terms of maximum pain relief) to morphine and, therefore, the suggested methadone dose in the treatment of postoperative pain would be approximately 10 mg. Following iv administration of this dose, the blood methadone concentration would rapidly decline because of the rapid distribution phase, and would be only slightly above the minimum effective analgetic blood methadone concentration at the commencement of the long terminal elimination phase. Therefore, the duration of analgesia would be expected to be much shorter than observed in the present study. By cautiously increasing the dose (to 20 mg), the difference between the minimum effective concentration and the blood methadone concentration at the commencement of the elimination phase would be greater, resulting in prolonged analgesia as a result of the low methadone clearance. It is apparent that the results of this study do not support the literature reports[5,17,18] of equivalence of 10 mg methadone and 10 mg morphine. While it is true that morphine and methadone are equipotent when considering maximum pain relief, current studies concerning the equivalence of analgetic agents usually examine the area under pain relief-time curves. An examination of the results of table 1 when compared with the normally accepted analgesic effects of morphine would suggest that 10 mg morphine is not equivalent to 10 mg methadone when both pain relief and duration of analgesia are considered. Future studies comparing methadone with either morphine or meperidine will be necessary to provide such data. Another possibility explaining the discrepancy between this communication (which uses iv administration) and other literature reports (usually im administration) is the apparently slow methadone absorption from intramuscular injection (results to be published).

The results of this study provide initial evidence of a relationship between the blood methadone concentration and analgesic response. For example, the median minimum effective analgesic blood methadone concentration was 30 ng/ml for both Group 2 (non-narcotic) and Group 3 (narcotic) patients, with a range from approximately 20 to 50 ng/ml. This 2.5-fold range is slightly less than the fourfold range previously reported by Austin *et al.*[19] for pethidine, and would indicate the existence of an effective blood methadone concentration for analgesia, below which pain recurrs. Interestingly, there is a statistically significant ($P < 0.05$, Student's t test, unpaired) greater elimination half-life of patients of Group 2 when compared with patients of Group 3, which is consistent with the longer duration of analgesia associated with Group 2 patients (table 1).

Additional postoperative narcotic analgesia was required by 35% of patients in the present study. It is suggested that a conservative dose of any narcotic (*e.g.*, 50 mg/70 kg body weight im for pethidine or 7.5 mg/70 kg body weight im for morphine) be used in the first instance because there is still a significant blood meth-

§ Inturrisi CE: Clinical pharmacology of analgesics. Audio-Digest, Anesthesiology 23, No. 14.

adone concentration, despite the patients' complaint of pain. If this dose is tolerated without significant side effects, subsequent doses may be increased to the more conventional dose (*e.g.*, 75 mg/70 kg body weight im for pethidine and 10 mg/70 kg body weight im for morphine). Current studies are directed at using further but reduced methadone doses where additional narcotic is requested.

It is apparent that methadone has a distribution phase $t_{1/2}$ of 6.1 ± 5.7 min following iv bolus administration (table 2). This value is similar to the value reported for pethidine in volunteer subjects[20] (mean value of 7.6 min), but significantly shorter than the corresponding value for pethidine in a group of postoperative patients[21] (30 ± 28 min, mean ± SD) where postoperative pain was controlled with a pethidine infusion. The large oil/water partition coefficient for methadone is at least partially responsible for the rapid distribution half-life and the large volume of distribution at steady state ($V_{D_{ss}}$) of 410 ± 156 l (*i.e.*, 6.1 ± 2.4 l/kg). Both V_C and $V_{D_{ss}}$ were shown to be positively correlated ($P < 0.025$) with patient body weight (fig. 2). The methadone $V_{D_{ss}}$ is larger than the reported values for pethidine[21] (238 ± 104 l, *i.e.*, 3.8 l/kg) and morphine[22,23] (values range from 1.02 to 3.2 l/kg).

The methadone terminal half-life varies with a mean (±SD) value of 35 ± 22 h (range 9–87 h) which is 7–10 times longer than that reported for either morphine[22,23] or pethidine.[21] The methadone terminal half life was positively correlated with patient age (fig. 3*A*, r = 0.58, $P < 0.02$). This indicates that care should be exercised when administering methadone to elderly patients, particularly when large or repeated doses may be required. This relationship may explain the case report[15] of prolonged postoperative respiratory depression lasting 8 days in an 81 year old (43.7 kg) patient administered 30 mg of methadone during surgery involving replacement of the aortic valve.

The mean (±SD) methadone clearance is 178 ± 100 ml/min (*i.e.*, 2.7 $ml \cdot min^{-1} \cdot kg^{-1}$ body weight) which is significantly lower than the literature values reported for pethidine[21] (600 ± 135 ml/min) and morphine[22] (1.0 l/min). Although there was a relationship between methadone terminal half-life and patient age, no similar relationship existed between methadone clearance and patient age or methadone volume of distribution at steady-state and patient age. However, there was a highly significant (r = −0.83, $P < 0.002$) correlation between methadone clearance and the minimum effective blood methadone analgetic concentration (fig. 4). At the present time, we are unable to suggest why such a relationship should exist between the rate at which methadone is eliminated from the body and the minimum blood methadone concentration to control pain. Figure 3*B* shows that there is no relationship between patient age and the minimum effective analgetic blood methadone concentration.

It is apparent that the strength of the various correlation analysis (figs. 2 and 3), while being statistically significant, is insufficient to allow the accurate prediction of various parameters from the data, with the exception of the relationship between methadone clearance and the minimum effective analgetic blood methadone concentration (fig. 4). Multivariable regression analysis was performed on the more important variables of duration of analgesia and minimum effective analgetic blood methadone concentration in an attempt to improve the accuracy of prediction from the data.

The variables with the most influence on the dependent variable are added sequentially to the regression equation with statistical analysis after every addition.[9] In the examples presented in this communication, meaningful equations were obtained when three or four variables were included in the regression equation. The duration of analgesia was related to age of the patient and the Eysenck Personality Inventory, neuroticism (N), social conformity (L), and extroversion (E) scores. Of these variables, the neuroticism and social conformity scores together with patient age had most influence on duration of analgesia. In contrast, social conformity and extroversion scores together with patient weight had most influence on the minimum effective analgetic blood methadone concentration. Other studies have shown that neuroticism[19,24] and extroversion[19] scores have correlated with reported pain[24] and the maximum pethidine concentration still associated with pain.[19]

There were no serious side effects observed in the postoperative period. Nausea and/or vomiting occurred in 48% of patients but was controlled by conventional antiemetic therapy in all cases. This incidence is similar to that reported in postoperative patients[25] following either morphine (15 mg) or pethidine (100 mg) administered preoperatively.

The conclusions from this study are: (1) Prolonged postoperative analgesia (median duration of analgesia, 27 h, n = 23) is similar to the terminal half-life (35 ± 22 h) determined in the same patients following an appropriate dose of methadone (20 mg) (tables 1 and 2). (2) There is a relationship between blood methadone concentration and analgetic response. (3) It may be possible to predict the duration of postoperative analgesia following methadone using the proposed formula. However, a larger study is needed to substantiate these findings. (4) It may be possible to predict the minimum effective analgetic blood methadone concentration for postoperative pain using the formula proposed. Once

again a larger study is necessary to confirm or deny these relationships.

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