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Relationship Between Blood Meperidine Concentrations and Analgesic Response:

A Preliminary Report

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Variability in analgesic responses to intramuscularly administered meperidine has been related to variable and unpredictable blood concentrations after injection. However, the contribution of variability in the relationship between blood concentration and effect has not been examined. The present study was designed to determine the relationship between blood meperidine concentrations and analgesic effects in nine patients during the first two postoperative days. Pain was estimated by subjective bioassay. The blood concentration–effect curves were steep, with a difference of as little as 0.05 μg/ml between the mean concentrations associated with severe pain and those associated with effective analgesia. Each curve had two inflection points: the maximum concentration still associated with severe pain (MCP) (0.41 μg/ml, SD = 0.17, n = 76) and the minimum effective analgesic concentration (MEAC) (0.46 μg/ml, SD = 0.18, n = 19). Interpatient variability of MEAC was appreciable (coefficient of variation = 39 per cent) and intrapatient variability was also detected. Variable pain control following intermittent intramuscular injections was shown to be due not only to variation in absorption, as reported previously, but also to variation in the blood meperidine concentration–analgesic response relationships. However, correlations were found between MCP and neuroticism and extroversion scores from a personality inventory and physical variables. Thus, equations that allow prediction of an individual's MCP were derived by multivariable regression. A blood meperidine concentration of 0.7 μg/ml would be expected to provide freedom from severe pain in approximately 95 per cent of cases. An intravenous infusion regimen for achieving and maintaining this concentration is described. (Key words: Analgesics, narcotic: meperidine. Pain: measurement; postoperative. Pharmacokinetics.)

TREATMENT OF SEVERE PAIN by repeated intramuscular injections of narcotics results in variable analgesic responses.[1,2] Our previous work has established a direct relationship between pain relief and blood concentrations of meperidine for patients who have postoperative pain.[3,4] Because of the steepness of the slope of the curve reflecting the blood concentration–effect relationship,[4] fluctuating blood concentrations necessarily mean variable responses. Blood concentrations of meperidine following repeated intramuscular injections fluctuate in phase with the dosing interval and are unpredictable due to highly variable absorption from the intramuscular depot.[4] However, our earlier study was designed to provide primary information about the variability of blood concentrations rather than the relationship between concentration and effect, so the dosing interval between injections was fixed (four hours). That study indicated that intramuscular injections *per se* were a major cause of the variability of blood concentrations and hence, clinical responses.

Unfortunately, the relationship between blood meperidine concentrations and analgesic responses is still poorly understood, and its stability unknown. Knowledge about the inter- and intrapatient variability of the minimum analgesic concentration is an important factor in the design of any dosage regimen, but especially those for intravenous infusion systems. Although those factors that may influence the relationship are ill-defined, personality recently has been shown to be an important determinant in postoperative analgesia.[5]

The aims of the present study were to determine the relationship between blood meperidine concentrations and analgesic responses for individual patients; to determine inter- and intrapatient variability of the relationship (especially the minimum analgesic concentration) and hence its contribution to the variability in responses seen clinically; and to seek simple predictors of the minimum analgesic concentration of meperidine needed for severe postoperative pain.

Materials and Methods

Informed consent was obtained from nine patients scheduled for surgical procedures usually associated with severe postoperative pain (table 1). Patients' ages ranged from 25 to 63 years and their body weights ranged from 65 to 93 kg. Patients were premedicated with diazepam (10 mg) administered orally 1.5 hours before operation. The left subclavian vein was cannulated via the antecubital fossa and the catheter was fitted with a double three-way stopcock for serial blood sampling. All surgical procedures commenced at 8 A.M.

Standard anesthetic management included ad-

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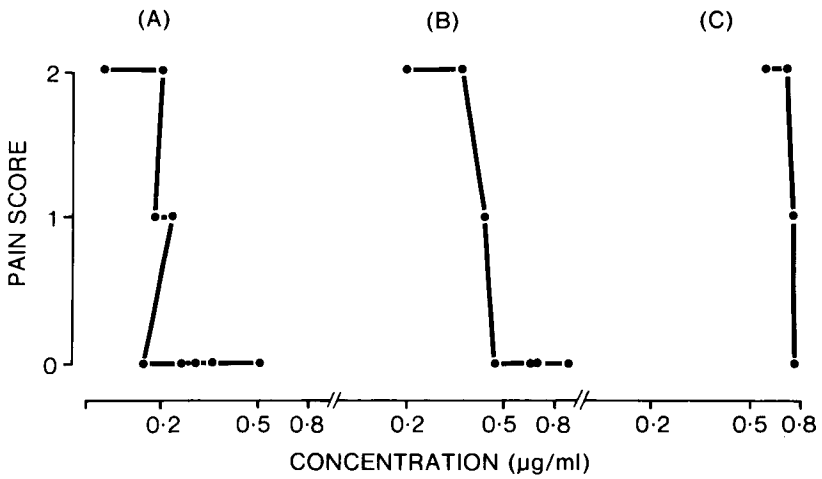

FIG. 1. Blood meperidine concentration–response curves for three individual patients, illustrating a typical range in interpatient responses. A = Patient 4, injection 6; C = Patient 1, injection 9; B = an additional patient studied in a pilot series whose concentration response data were identical to the mean of the present series.

ministration of atropine, thiopental, nitrous oxide–oxygen, muscle relaxants, and halothane, and control of respiration. Analgesic drugs were not administered before or during anesthesia.

Postoperatively, each patient received meperidine HCl, 75 mg, injected intramuscularly into the buttock soon after arrival in the recovery room and subsequently when needed until early evening. Overnight, the patient was left undisturbed, and received meperidine HCl, 100 mg, by intramuscular injection as required. The next day, approximately 20 hours after cessation of the surgical procedure, patients received meperidine HCl, 75 mg, as before. A minimum dosing interval of 1.5 hours was set for safety reasons.

Samples of subclavian venous blood were taken before each injection and then at 30-minute intervals until a further injection was requested. When a patient requested analgesic medication overnight, a blood sample was taken by the nursing staff and the time of the request recorded. Blood meperidine concentrations were determined using previously reported methods and were expressed as meperidine base.[3]

Pain was also estimated by the patient at 30-minute intervals during the daytime. Scores from the patients' responses to a brief questionnaire[3,4] were assigned as follows: 2 = severe pain, 1 = moderate pain, 0 = no pain.

The Eysenck personality inventory, which measures neuroticism (N), extroversion (E), and social conformity or lie (L), has been used by others in postoperative pain assessment.[5] This questionnaire was completed by each patient in about 4 minutes on the evening before operation.[6]

Statistical Package for the Social Sciences[7] (version 7.01, 1977) was used on a digital computer (Digital Equipment Corporation DEC system 10) to provide descriptive statistics (subprogram CONDESCRIPTIVE); analysis of variance (subprograms ONEWAY and NPAR TESTS); correlation analysis (subprogram NONPAR CORR); multivariable regression (subprogram REGRESSION); and partial correlation analysis (subprogram PARTIAL CORR). Specific tests utilized by these programs were the Kruskal-Wallis one-way analysis of variance, the Mann-Whitney U test, the Spearman nonparametric correlation analysis, and Student's *t* test.

TABLE 1. Patient Characteristics

	Operation	Age (Years), Sex	Body Weight (Kg)	Height (cm)	Lying Girth (cm)	Standing Girth (cm)
Patient 1	Cholecystectomy	28, F	66	157	91	83
Patient 2	Arthrotomy	25, M	93	186	88	92
Patient 3	Cholecystectomy	58, F	65	169	86	92
Patient 4	Cholecystectomy	63, M	89	169	97	99
Patient 5	Cholecystectomy	54, M	84	168	102	100
Patient 6	Hysterectomy	38, F	74	181	94	84
Patient 7	Patellectomy	34, F	68	182	75	83
Patient 8	Arthrotomy	61, F	70	162	97	98
Patient 9	Cholecystectomy	42, M	73	173	93	96
MEAN		45	76	172	91	92
SD		15	10	10	8	7

Results

Variability of the Blood Concentration–Response Relationship

Practically all injections studied resulted in curves qualitatively similar to those presented in figure 1. Inter- and intrapatient variability of the blood meperidine concentration–analgesia relationship were evaluated by determining three key points (table 2): 1) the maximum blood concentration still associated with severe pain (MCP) was identified as an inflection point and represented the concentration above which some analgesia was achieved; 2) the minimum effective analgesic concentrations (MEAC) represented a second inflection point, where a patient perceived a transition from some pain (score = 1 or 2) to effective analgesia; 3) the midpoint between these two points of inflection, the concentration associated with partial analgesia (score = 1), was also recorded.

Interpatient variability associated with all three points was relatively large. The mean MCP over 76 injections was 0.41 μg/ml (SD = 0.17, CV = 42 per cent), with a range of 0.1 to 0.98 μg/ml. Mean MEAC was 0.46 μg/ml (SD = 0.18, CV = 39 per cent; range 0.24–0.76 μg/ml) determined over 19 complete cycles of transition from severe pain to effective analgesia. Effective analgesia was not achieved after many of the injections, thus accounting for the apparent discrepancy in the numbers of injections studied.

Table 2. Blood Meperidine Concentrations and Analgesic Responses

	Severe Pain (Score = 2)				Moderate Pain (Score = 1)				Effective Analgesia (Score = 0)					Number of Injections Studied Intensively
	Meperidine* (μg/ml)		CV (Per Cent)	n	Meperidine† (μg/ml)		CV (Per Cent)	n	Meperidine‡ (μg/ml)		Specific Injections	CV (Per Cent)	n	
	Mean	SD			Mean	SD			Mean	SD				
Patient 1	0.48	0.12	25	11	0.58	0.16	28	6	0.70	0.10	0.58 0.76 0.76	14	3	7
Patient 2	0.45	0.12	27	11	0.44	0.16	36	7	0.64	0.10	0.52 0.72 0.67	16	3	7
Patient 3	0.53	0.27	51	6	0.59	0.30	51	2	0.70		0.70		1	3
Patient 4	0.20	0.04	20	6	0.25	0.07	28	4	0.27	0.04	0.24 0.29	15	2	4
Patient 5	0.35	0.15	43	8	0.38	0.13	34	4	0.36	0.09	0.39 0.44 0.26	25	3	5
Patient 6	0.36	0.09	25	10	0.41	0.05	12	5	0.42		0.42		1	6
Patient 7	0.54	0.13	24	10	0.59	0.07	12	4	—					5
Patient 8	0.40	0.17	43	9	0.37	0.18	49	5	0.37	0.10	0.38 0.25 0.36 0.49	27	4	5
Patient 9	0.20	0.06	30	5	0.22	0.06	27	4	0.30	0.03	0.28 0.32	10	2	4
Grand mean	0.41	0.17		76	0.42	0.17		41	0.46	0.18			19	

* Maximum blood meperidine concentration associated with severe pain (MCP).

† Maximum blood meperidine concentration associated with moderate pain.

‡ Minimum blood meperidine concentration associated with effective analgesia (MEAC).

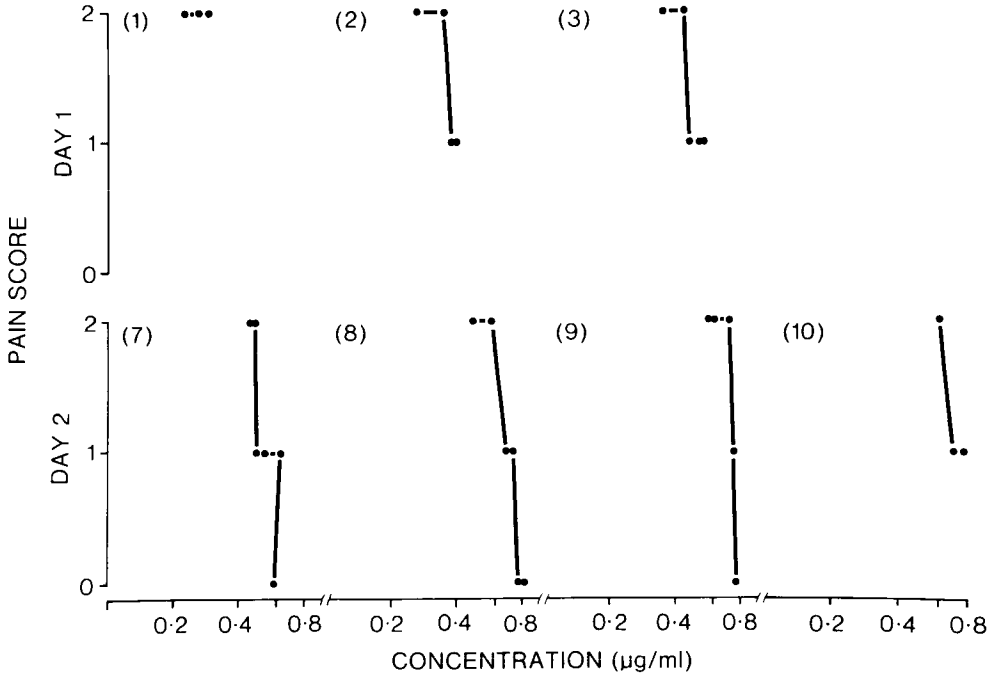

FIG. 2. A series of blood meperidine concentration–response curves for one patient illustrating the consistency of intrapatient responses. Numbers in brackets refer to the injection numbers (three injections were given overnight).

Interpatient variability in the midpoint between these two inflection points was also relatively high (mean = 0.42 μg/ml, SD = 0.17, n = 41).

Intrapatient variability over two days for the three key points was less than interpatient variability (table 2). The coefficients of variation of MCP for individuals ranged from 20 to 51 per cent. Variability in individual minimum effective analgesic concentrations was difficult to quantitate because of insufficient data. Individual MEACs for Patient 8, for example, ranged from 0.25 to 0.49 μg/ml. The intrapatient coefficient of variation in the midpoint between the two inflection points was 31 per cent (SD = 14 per cent, n = 9). No significant trend in any of these key concentrations could be demonstrated over the two days studied. Patient 7 failed to achieve effective analgesia after five of the injections studied. Estimates taken overnight when analgesia was requested were included with the other estimates of MCP (*i.e.*, the inflection point when patients who were previously analgesic reported severe pain).

Although the shapes of concentration–effect curves for different patients were qualitatively similar, individual curves were found to shift to the left and to the right of the mean relationship, resulting in a fourfold range (fig. 1). Intrapatient variability was confined to minor shifts, and individual curves were relatively consistent for most patients. However, blood concentrations often were inadequate for the complete range of responses to be observed. As concentrations increased with repeated injections, individual MEACs could be determined. A series of seven estimates of the concentration–effect relationship for Patient 1 (three estimates on the day of operation and four on the following day) is shown in figure 2.

The significance of the contribution of variability in MEACs to variability in analgesic responses can be appreciated when the means and standard deviations of MEAC are superimposed on blood meperidine concentrations reached after intramuscular injections[4] (fig. 3).

Patient Personality, Postoperative and Physical Characteristics

Individual personality inventories are presented in table 3. Although the number of patients studied was small, a range of scores was obtained: neuroticism (N) = 6–21; extroversion (E) = 3–14; lie (L) = 2–7. The number of injections requested over the 32-hour study, the total number of injections given postoperatively, the average dosing interval, and the time from cessation of surgical intervention to the first request for analgesia are also shown in table 3. Mean dosing intervals for individuals ranged from 2 to 5 hours, and the times to request the first injection from 15 to 105 minutes.

Correlations between MCP, personality scores, postoperative characteristics, and physical variables were sought, and these are summarized in table 4. Because of the small number of patients, correlations with probability values up to 0.1 are included in

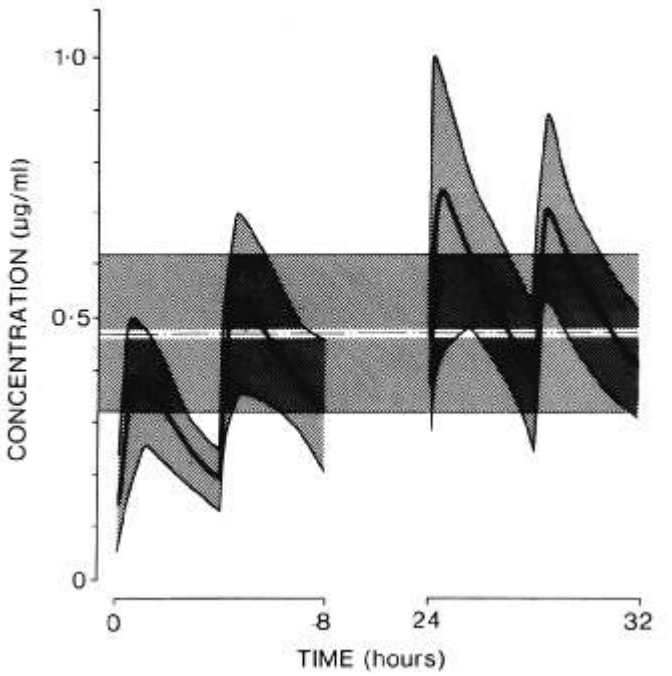

FIG. 3. Composite diagram showing the mean (—·—) ± 1 SD (\\\) of the minimum effective blood concentration of meperidine obtained from the present study (0.46 ± 0.18 g/ml) superimposed on blood meperidine concentrations mean (——) ± 1 SD (///) attained from four-hourly 100-mg intramuscular doses of meperidine in a previous study.[4]

the summary. The MCP was negatively correlated with lying girth, standing girth (both measured at the umbilicus) and mean dosing interval, and was positively correlated with E. A negative correlation between body weight and MCP was also found, ($r = -0.628$) with a level of significance of 0.07.

Neuroticism was positively correlated with the total number of injections given postoperatively and extroversion negatively with lying girth. Several other correlations with physical variables were noteworthy: lying girth positively with mean dosing interval; standing girth negatively with mean dosing interval and positively with age; age negatively with the number of injections given during the first 32 hr postoperatively; and E positively with mean dosing interval and L. Although MCP was correlated with lying girth, lying girth with E, and MCP with E, partial correlation analysis failed to indicate intrinsic correlations between specific pairs.

PREDICTION OF MCP

Prediction of MEAC itself was not attempted because of the relatively small number of successful estimations obtained. The protocol resulted in numerous injections of meperidine that did not yield a full range of responses; thus, the MEAC was not reached in 27 of 46 detailed response curves studied. Since it was shown that, in all cases, an extremely narrow range of concentrations were associated with the transition from MEAC to MCP in the meperidine concentration–response relationship, and since more numerous estimates of MCP for individuals were available, retrospective multivariable regression and estimation of MCP rather than MEAC were attempted (table 5).

Using only the mean MCP estimated from 76 dosing intervals as a predictor resulted in a mean error (±SD) of -0.02 ± 0.13 μg/ml with a range of error of 0.34 μg/ml (table 5). Estimates of MCP based on lying girth reduced the range of error to 0.26 μg/ml. More complex equations incorporating lying girth, N, and E reduced the mean error (±SD) to 0 ± 0.07 μg/ml, and those incorporating lying girth, N, E, height, and body weight reduced it to 0 ± 0.06 μg/ml. The most complex equation resulted in a mean error (±SD) of 0 ± 0.03 μg/ml.

Discussion

A relationship between blood meperidine concentrations and analgesia in patients suffering postoperative pain has been established.[3,4] The minimum analgesic concentration appears to be independent of the method of drug delivery, being the same whether determined during intravenous infusion or intramuscular injections. In the first instance, patients progressed from severe pain to analgesia, while in the second instance, patients fluctuated from severe pain to pain-free and then back to severe pain. These previous studies, however, were not designed to derive information about the relationship itself. The present study was designed to confirm the nature of the relationship between blood meperidine concentrations and

TABLE 3. Patient Personality Inventory and Postoperative Variables

	Personality Inventory*			Number of Injections over 32 Hours	Total Number of Injections	Mean Dosing Interval† (Hours)	Time before First Request (Min)
	N	E	L				
Patient 1	21	11	4	11	20	2.8	15
Patient 2	7	12	2	12	18	2.7	66
Patient 3	19	10	6	8	15	3.4	38
Patient 4	6	7	7	7	9	3.5	50
Patient 5	7	10	4	8	11	3.8	26
Patient 6	9	3	3	11	15	3.0	33
Patient 7	4	14	6	9	9	2.2	31
Patient 8	16	7	5	9	12	3.4	46
Patient 9	7	8	3	7	9	5.3	105

* N = neuroticism score (0–24); E = extroversion score (0–24); L = lie or social conformity score (0–9).

† Mean dosing interval refers to the time between requests for injections over the 32-hour study period.

analgesic effects and to determine the relative contribution that variability of the relationship makes to variability of clinical responses.

Low concentrations of meperidine (<0.1 μg/ml) do not alter the perception of pain. When the blood concentration is increased gradually, a critical concentration is encountered where a small further increase (~0.05 μg/ml, table 2) can result in patients' becoming completely analgesic. The narrowness of this concentration range for individuals (previously reported for mean data) was surprising. The concentration–effect curves within and among patients are consistent; only the relative positions of the curves left or right along the blood meperidine concentration axis change, resulting in variable minimum effective analgesic concentrations. The minimum analgesic concentrations are relatively stable with time for any individual (fig. 2). Differences among patients, on the other hand, may be quite large (fig. 1). Possible reasons for inter- and intrapatient differences include: the interpretation of the term "blood concentration" (*e.g.*, neither plasma protein binding nor erythrocytic uptake of meperidine was measured); concomitant nonanalgesic medications administered; differences in individual patients' interpretations of pain intensity; and individual patients' different expectations (including uncontrollable factors such as psychological, diurnal, or even environmental).

Although the number of patients in this study was small, the results reveal no tendency for the MEAC to be dependent on the type of surgical procedure studied. Variation in MEACs for cholecystectomy appears similar to that reported for hysterectomy, and present results for arthrotomy and a patellectomy.

TABLE 4. Correlations Between Maximum Blood Meperidine Concentration Still Associated with Severe Pain (MCP), Patient Physical Characteristics, and Postoperative Variables

	Spearman's r	P*
Maximum concentration associated with severe pain		
With lying girth	−0.786	≤0.01
With standing girth	−0.726	≤0.03
With extroversion score	0.671	≤0.05
With body weight	−0.628	≤0.07
With mean dosing interval	−0.798	≤0.01
Personality		
Neuroticism score		
With total injections	0.762	≤0.02
With height	−0.596	≤0.09
Extroversion score		
With MCP	0.671	≤0.05
With age	−0.639	≤0.06
With lying girth	−0.675	≤0.05
Lie score with age	0.650	≤0.06
Physical characteristics		
Lying girth		
With mean dosing interval	0.668	≤0.05
With MCP	−0.786	≤0.01
With extroversion score	−0.675	≤0.05
Standing girth		
With number of injections (32 hr)	−0.611	≤0.08
With mean dosing interval	0.798	≤0.01
With MCP	−0.726	≤0.03
With age	0.714	≤0.03
Age		
With number of injections (32 hr)	−0.746	≤0.02
With mean dosing interval	0.678	≤0.05
With extroversion score	−0.639	≤0.06
With lie score	0.650	≤0.06
With standing girth	0.714	≤0.03
Height with neuroticism score	−0.596	≤0.09
Body weight with MCP	−0.628	≤0.07

* Two-tailed probability.

TABLE 5. Prediction of Maximum Meperidine Concentration Still Associated with Severe Pain (MCP)*

	Mean MCP μg/ml	Estimate ϕ		Estimate 1		Estimate 2		Estimate 3		Estimate 4	
		μg/ml	Δ†	μg/ml	Δ	μg/ml	Δ	μg/ml	Δ	μg/ml	Δ
Patient 1	0.48	0.41	0.07	0.39	0.09	0.51	−0.03	0.49	−0.01	0.49	−0.01
Patient 2	0.20	0.41	−0.21	0.37	−0.17	0.33	−0.13	0.33	−0.13	0.24	−0.04
Patient 3	0.45	0.41	0.04	0.43	0.02	0.42	0.03	0.47	−0.02	0.44	0.01
Patient 4	0.53	0.41	0.12	0.45	0.08	0.53	0	0.55	−0.02	0.57	−0.04
Patient 5	0.20	0.41	−0.21	0.33	−0.13	0.28	−0.08	0.20	0	0.22	−0.02
Patient 6	0.35	0.41	−0.06	0.28	0.07	0.28	0.07	0.30	0.05	0.36	−0.01
Patient 7	0.40	0.41	−0.01	0.33	0.07	0.37	0.03	0.36	0.04	0.33	0.07
Patient 8	0.36	0.41	−0.05	0.36	0	0.28	0.08	0.32	0.04	0.36	0
Patient 9	0.54	0.41	0.13	0.57	−0.03	0.52	0.02	0.49	0.05	0.52	0.02
MEAN			−0.02		0		0		0		0
SD			0.13		0.10		0.07		0.06		0.03
RANGE			0.34		0.26		0.21		0.18		0.11

* Estimate ϕ: MCP = 0.41 (table 2);
Estimate 1: MCP = 1.365 − 0.011 Lygirth;
Estimate 2: MCP = 0.948 − 0.008 Lygirth + 0.010 N + 0.011 E;
Estimate 3: MCP = −1.612 + 0.002 Lygirth + 0.016 N + 0.024 E + 0.010 Ht − 0.004 BWt;
Estimate 4: MCP = −5.027 + 0.023 Lygirth + 0.022 N + 0.045 E + 0.022 Ht − 0.007 BWt + 0.046 L − 0.009 StGirth; where Lygirth = lying girth (cm); StGirth = standing girth (cm); N, E, L = personality inventory scores; Ht = height (cm); BWt = body weight (kg). Equations were determined by multivariable regression.

† Δ = difference between observed and estimated MCP.

Any differences in intensity of pain speculated to occur from different operating sites may be too small to detect by current methods, but in practice a blood meperidine concentration of 0.6 μg/ml would have provided freedom from severe pain in 84 per cent of the 76 dosing intervals studied, including dosing intervals after cholecystectomy, hysterectomy, arthrotomy and patellectomy. A blood concentration of 0.7 μg/ml would have resulted in freedom from severe pain in 95 per cent of cases. This concentration may be reached and maintained reliably using an intravenous infusion regimen described recently.[3] An extension of this study to determine whether differences in the MEACs for different operative sites (*e.g.*, major abdominal, *c.f.* orthopedic) needs to be undertaken. However, preliminary results in table 2 suggest that interpatient variability in MEACs will be greater than differences resulting from different operative sites.

The significance of these results can be appreciated when considering individualization of clinical pain management, especially when intravenous infusion techniques are used to reduce the large variability in blood concentrations associated with intramuscular absorption. Individualization of pain management has two prerequisites. First, because of the nature of the relationship between analgesia and blood meperidine concentrations, blood concentrations need to be predictable, stable and controlled. Second, the MEAC for a particular patient also should be predictable to enable design of a rational intravenous infusion regimen that would result in blood concentrations above this minimum. Variable absorptions from intramuscular injections of meperidine result in inadequate, fluctuating, and unpredictable blood concentrations. However, not only are blood concentrations provided by intravenous infusion regimens stable,[3] but recent work has shown that they are also predictable from simple physical variables.[8] Hence the first prerequisite is satisfied.

Previous investigators have sought simple correlations between age and blood meperidine concentrations,[9] age and number of doses given for severe pain,[10] and personality scores and postoperative pain.[5] Our results are in general agreement with those reported earlier and in addition, our approach has taken one step further. This study yielded correlations between the maximum blood concentration of meperidine still associated with severe pain (MCP) and other simple variables such as personality inventory scores and physical variables. Because of the extremely steep slope of the curve of the blood concentration–analgesic response relationship, this MCP is a reasonable (but slightly lower) approximation of the analgesic concentration (MEAC). Due to paucity of data describing MEAC, MCP was chosen for predictive analysis. The statistical technique of multiple variable analysis was used to derive simple equations to predict this value. Thus, the second prerequisite is now realizable, providing the possibility of complete individualization of analgesic requirements.

Analgesic responses following intramuscular injection of narcotics are highly variable. Previous studies attributed this to unpredictability of blood concentrations resulting from variable absorption. We now conclude that variation in the blood concentration–effect relationship itself is a significant factor in the production of variable clinical responses, but that individual minimum effective analgesic concentrations may be largely predictable from personality inventory scores and physical variables.

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