THE MINIMUM EFFECTIVE ANALGETIC BLOOD CONCENTRATION OF PETHIDINE IN PATIENTS WITH INTRACTABLE PAIN

LAURENCE E. MATHER & CHRISTOPHER J. GLYNN*

Department of Anaesthesia & Intensive Care, Flinders Medical Centre,
The Flinders University of South Australia, Bedford Park, South Australia, 5042.

- 1 Pethidine infusions were performed in 16 patients with intractable pain in order to define a minimum effective analgetic blood concentration (MEAC) range.
- 2 Pethidine blood concentrations at the return of pain following a period of analgesia were considered to provide a more useful estimation of the MEAC than that at the onset of analgesia.
- 3 The MEAC range found in 15 of the 16 patients was 0.10 mg/l to 0.82 mg/l (median 0.25 mg/l). The intravenous dose of pethidine used in this study did not provide analgesia in one patient.
- 4 If the MEAC was greater than 0.40 mg/l in any patient, then additional techniques were required to provide adequate long term analgesia, e.g. destructive neurolytic techniques or antidepressant therapy.
- 5 The pharmacokinetic properties of pethidine found in the majority of these patients were in the range considered to be normal.
- 6 The clinical pharmacokineticist has an important role to play in the investigation, diagnosis and treatment of patients with intractable pain by detecting those patients with atypical pharmacokinetic and/or pharmacodynamic characteristics towards analgesic drugs.

Introduction

Since systemically administered opioid analgesic agents are transported to their receptors by the blood, it may be presumed that there is relationship between the opiate concentration in the blood and the receptor concentration which produces analgesia. If there is a minimum receptor concentration of opioid consistent with the patient's report of analgesia it is reasonable to assume that there is a particular blood concentration which reflects this receptor concentration. This is analogous to the relationships demonstrated between circulating opioid concentrations and the degree of respiratory depression (Hug & Murphy, 1979; Hug *et al.*, 1981). Thus, we have defined the minimum effective analgetic (blood) concentration (MEAC) of an opioid analgetic agent as the lowest (blood) concentration of that agent consistent with the patient's report of complete analgesia. It therefore seems pertinent, clinically, to define the MEAC for a patient with intractable pain and to make use of this value in evaluating dosage regimens for that patient.

Previous studies with pethidine in patients with post-operative pain have defined a range for MEAC

(Stapleton *et al.*, 1979; Austin *et al.*, 1980). In other studies it has been shown that the MEAC for patients with intractable pain remained similar for periods of up to a year (Glynn & Mather, 1982). For the purposes of this study, intractable pain is defined as pain of at least one month's duration which has not been relieved by conventional techniques.

The International Association for the Study of Pain has defined pain as an '*unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage*' (Merskey *et al.*, 1979). However, recent evidence has suggested that reports of the unpleasant mood factors anxiety, aggression and depression are intimately related to the report of intractable pain (Glynn *et al.*, 1981). Thus it is important to define the MEAC in terms of transition from the absence of pain to the first report of pain because any qualification of the pain report involves '*psychological*' (emotional) interpretation (Littlejohns & Vere, 1981). Indeed, the MEAC in two patients who became habituated on and apparently tolerance to pethidine did not change, suggesting that habituation and tolerance was due to effects other than the analgetic effect of pethidine (Glynn & Mather, 1982).

The aims of the present study were:

1. To examine blood concentrations at the onset and

*Present address: Centre for Pain Relief, Abingdon Hospital, Abingdon, Oxon.

offset of analgesia after an intravenous bolus of pethidine and to compare these two estimations of the MEAC.

2. To establish an MEAC range for pethidine in patients with intractable pain.
3. To study pharmacokinetic characteristics of pethidine in patients with intractable pain.
4. To evaluate the usefulness of pharmacodynamic and the pharmacokinetic data obtained in the design of effective analgesic regimens for the patients studied.

Methods

Informed consent was obtained from all patients after explanation of the procedures involved. There were 6 female and 10 male patients with an age range of 25 to 70 years (Table 1). The diagnoses believed to be the cause of the intractable pain in each of these patients are shown in Table 1 and comprised 12 patients with carcinoma and 4 patients with non-malignant conditions. Analgesic administration was stopped at least 8 h before the study. All patients were fasted for a minimum of 4 h before the study. Studies were conducted in a high dependency area of the hospital with a qualified nurse observer in attendance throughout the study.

Under local anaesthesia with procaine, a central venous catheter was inserted via the cubital fossae of the non-dominant arm for blood sampling. However, arterial cannulae were placed in two patients and these were used for blood sampling. An intravenous cannula was placed in the dorsum of the contra-

lateral hand for drug administration. Pethidine HCl 100 mg diluted to 12 ml in physiological saline was injected via the peripheral intravenous cannula over 60 s. Accurate 1 ml blood samples were taken at the bedside using 1 ml insulin syringes and a double 3-way tap system. These were collected via the central venous or arterial line at 2, 5, 10, 20, 30, 40, 50, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330 and 360 min after the injection and stored in ice. Blood concentrations of pethidine and norpethidine were measured by gas liquid chromatography using nitrogen selective detectors (Mather & Tucker, 1974). Pharmacokinetic parameters for pethidine were obtained from empirical polyexponential curves fitted to the blood concentration-time data as previously described (Austin *et al.*, 1981a). The nurse collected the blood samples at each time and asked the patient to report the level of pain on a score of 2 = 'normal' pain, 1 = partial relief and 0 = no pain (Stapleton *et al.*, 1979). Records were kept of pulse rate, blood pressure, respiratory rate and any other symptom volunteered by the patient. It was possible to obtain two estimates of the 'analgesic blood concentrations' of pethidine for each patient: (1) at the onset of analgesia and (2) at the return of pain. Thus, analgesia equated with report of no pain by the patient or 0 on the scale used.

Results

Blood concentration-response relationships

The blood concentration of pethidine at the onset of

Table 1 Patient data

Patient number	Age (years)	Sex	Weight (kg)	Diagnosis	Post-study treatment
1	40	M	86	Post-traumatic neuralgia	Oral and rectal pethidine
2	50	M	52	Chronic pancreatitis	Oral and rectal pethidine
3	40	F	50	Scleroderma	Intramuscular pethidine
4	25	M	66	Angioma of the spinal cord	Local anaesthetic nerve blockade
5	64	M	90	Carcinoma of the lung	†Oral narcotics
6	47	F	53	Carcinoma of the colon	Oral and rectal pethidine
7	50	M	68	Carcinoma of the lung	†Oral narcotics
8	67	M	52	Carcinomas of the stomach and lung	*Bilateral splanchnic nerve blockade
9	51	F	52	Carcinoma of the colon	Oral and rectal pethidine
10	58	M	80	Multiple myeloma	Oral and rectal pethidine
11	53	M	40	Carcinoma of the lung	†Oral narcotics
12	43	M	88	Carcinoma of the lung	Oral and rectal pethidine
13	70	M	65	Carcinoma of the lung	†Oral narcotics
14	53	F	45	Carcinoma of the adrenal	*Bilateral splanchnic nerve blockade
15	43	F	56	Carcinoma of the breast	Antidepressants
16	54	F	80	Renal cell carcinoma	†Intrathecal phenol and oral narcotics

* Destruction of the splanchnic nerves with phenol.

† Indicates patients who had been treated previously with other narcotics (morphine, dextromoramide) and who felt that these narcotics provided better quality of analgesia than did pethidine.

analgesia (score 0) and the time taken to achieve this for each patient is shown in Table 2. The range of analgetic blood concentrations for the patients with venous blood samples was 0.38 mg/l to 2.94 mg/l with a median of 0.77 mg/l. The time taken to onset of analgesia in these patients varied from 2 min to 90 min with a median time of 15 min. Values for the patients (numbers 13, 15) with arterial blood samples are included in Table 2 but are not strictly comparable. The blood concentration of pethidine at the return of pain (score 1) and the duration of analgesia for each of the patients are also shown in Table 2. The range of analgetic blood concentrations found at the time was from 0.10 mg/l to 0.82 mg/l with a median of 0.25 mg/l. The duration of analgesia in these patients varied from 0 min to 355 min with a median of 105 min. One patient (number 16) did not achieve complete analgesia following the intravenous bolus of pethidine HCl 100 mg despite having a blood concentration of 0.89 mg/l 2 min after injection.

Pharmacokinetic characteristics

The pharmacokinetic parameters calculated from the blood concentrations obtained for these patients are shown in Table 2. For the majority of patients the data were described by a classical two compartment

open model but for some this simplified to a one compartment system. The initial volume of distribution of pethidine in the patients with venous sampling varied from 21 l to 210 l with a median of 84 l but was considerably lower for the two patients with arterial sampling. The volume of distribution at steady-state for all patients varied from 77 l to 289 l with a median of 177 l and total body clearance of pethidine varied from 0.27 l/min to 1.54 l/min with a median of 0.73 l/min. The fast (or redistribution) half-life of pethidine in the 10 patients with venous sampling varied from 1 min to 21 min with a median of 5 min. The slow (or elimination) half-life varied from 103 min to 401 min with a median of 191 min. No redistribution phase was detected in four patients (numbers 2, 4, 8, 14). Values of pharmacokinetic constants derived from arterial sampling (patient numbers 13 and 15) cannot be compared to the values derived from venous sampling with the exceptions of total body clearance and volume of distribution at steady-state which are independent of sampling site in the arm.

Clinical effects

No patient showed any sign of respiratory depression judged by a respiratory rate of less than 10 breaths/min during the study. There were no significant

Table 2 Pharmacodynamics and pharmacokinetics of pethidine in patients with intractable pain

Patient number	Onset of analgesia Blood concentration (mg/l)	Time to onset (min)	Offset of analgesia Blood concentration (mg/l)	Duration of analgesia (min)	V_D^1 (l)	V_{DSS}^2 (l)	CL^3 (l/min)	$t_{1/2}$ fast (min)	$t_{1/2}$ slow (min)
1	0.31	50	0.31	60	41	217	1.27	1	126
2†	0.40	5	0.23	90	181	181	0.74	—	162
3	0.30	15	0.24	90	60	213	0.76	1	198
4†	0.42	35	0.21	210	210	212	0.64	—	252
5	0.77	90	0.30	150	21	125	0.91	21	104
6	2.94	15	0.28	90	91	162	0.86	1	159
7	0.38	30	0.25	60	106	289	0.50	7	252
8†	0.51	5	0.20	355	173	173	0.47	—	255
9	0.83	15	0.38	195	84	153	0.27	17	401
10	1.14	3	0.10	300	40	236	0.87	2	201
11	0.36	20	0.21	220	91	167	0.53	8	224
12	0.80	15	0.17	165	84	221	0.82	8	203
13*	1.44	20	0.30	120	15	87	0.71	1	103
14†	1.58	2	0.82	18	77	77	0.36	—	168
15*	1.69	10	0.66	70	10	138	0.61	2	183
16	0.89	— partial analgesia —		0	53	241	1.54	1	114
Median	0.77	15	0.25	105	84	177	0.73	2	191
Range	0.38 2.94	2 90	0.10 0.82	0 355	21 210	77 289	0.27 1.54	1 21	103 401

* Arterial samples obtained.

† Pethidine pharmacokinetics were described by a one compartment open model in these patients.

¹ V_D = initial dilution volume.

² V_{DSS} = volume of distribution at steady-state equilibrium

³ CL = mean total body clearance.

changes in pulse rate or blood pressure in any patient during the study. Three patients complained of nausea which disappeared after about 20 min without treatment and one patient vomited. Two patients complained of dizziness which was not associated with any blood pressure change and which settled within 20 min.

Post-study treatment

Subsequently six patients (numbers 1, 2, 6, 9, 10, 12) were successfully treated with oral and rectal pethidine for their pain (Table 1). One patient (number 3) reported in detail elsewhere (Glynn & Mather, 1982) had poor oral and rectal bioavailability of pethidine but was successfully treated with intramuscular pethidine (Table 1). Four patients (numbers 5, 7, 11, 13) did not obtain adequate relief from oral and rectal pethidine but did obtain analgesia from the use of other narcotics (Table 1). One patient (number 4) was successfully treated with repeated local anaesthetic nerve blocks while another patient (number 15) required antidepressants. Three patients were treated with neurolytic nerve ablation, two (numbers 8, 14) required no further narcotic analgesia and one (number 16) required oral narcotics as well (Table 1).

Discussion

This study has defined a minimum effective analgetic blood concentration for pethidine in 15 of the 16 patients studied—the remaining patient failed to achieve complete analgesia. The return of pain following the analgesia provided by the intravenous pethidine was associated with lower blood concentrations than at the onset of analgesia and is by definition the minimum effective analgetic blood concentration of pethidine (Table 2). The relationship is not unexpected as it is more likely that the blood concentration during the elimination phase reflects the 'receptor' concentrations better than during the redistribution phase, because the elimination phase represents a pseudo-equilibrium state within the body. If this is so, then these blood concentrations provide a therapeutically useful characteristic for this drug.

It can be argued legitimately that measurement of pethidine concentrations in plasma water would be a more appropriate value to correlate with clinical effect. However, since the ratio of blood to plasma concentrations and the fraction unbound in plasma do not change markedly over the concentration range of interest (Edwards *et al.*, 1982), then measurement of whole blood concentrations alone was used for both the pharmacokinetic and pharmacodynamic aspects of this study. Thus it is possible that some of the inter-patient variability in MEAC may be explicable in terms of differences in cellular uptake and

plasma binding. Furthermore, in retrospect, a slower loading infusion (say over 40 min) which allowed for concurrent body redistribution would have provided a more useful estimate of MEAC at the onset of analgesia. This modification has been incorporated into our clinical practice.

The reproducibility of the MEAC in individual patients first observed in patients with post-operative pain (Austin *et al.*, 1980) has been confirmed in a longitudinal study in which three of these patients (numbers 1, 2, 3) were studied over a period of months. Because of the clinical complexities of these patients, results are given in more detail in a separate report (Glynn & Mather, 1982). It was possible to design an effective analgetic pethidine regimen for seven of the patients in this study using MEAC data (Table 1). Four patients were successfully treated with other narcotics which these patients felt provided a better quality of analgesia than pethidine. The remaining two patients (numbers 4, 8), whose MEAC was less than 0.40 mg/l, were treated successfully with neural blockade.

The MEAC for patient number 14 was 0.82 mg/l and the duration of analgesia was only 18 min. Thus this patient differed considerably from the other patients studied and doses of pethidine required to maintain this MEAC value would have been large. Large oral doses of pethidine are associated with high norpethidine blood concentrations with a potential for adverse effects (Austin *et al.*, 1981b). A large oral dose of pethidine (600 mg) was administered in one patient (number 3) and resulted in norpethidine blood concentrations in excess of 1 mg/l and untoward side effects (Glynn, Mather, Gourlay & Walsh, submitted). A bilateral neurolytic splanchnic nerve block with phenol successfully diminished patient number 14's complaints of pain so that she was comfortable on a non-narcotic regimen. The MEAC for patient number 15 was 0.66 mg/l. At blood concentrations only slightly in excess of this, the patient was heavily sedated but complained of pain as soon as she awoke. This patient was referred to a psychiatrist who confirmed her depression which was treated successfully with antidepressants. Thus it would seem that in both these patients there was a significant emotional component to their pain and in this group of patients a MEAC of greater than 0.40 mg/l (Figure 1) was associated with a significant emotional component of pain on top of the sensory component. The last patient, number 16, did not obtain analgesia from the pethidine dose used, most probably because of the combination of high total body clearance (1.54 l/min) and an extensive redistribution phase which prevented adequate receptor concentrations from being achieved. Thus this patient did not achieve an MEAC (pharmacodynamic response), because of the high clearance (pharmacokinetic response), (Figure 1).

Figure 1 Pharmacodynamics and pharmacokinetics of pethidine in patients with intractable pain. The range of possible pharmacodynamic (MEAC) and pharmacokinetic (clearance) combinations in any patient with intractable pain. The shaded ordinate indicates the 'normal' range for the MEAC discerned for patients with intractable pain (0.2 mg/l to 0.4 mg/l) while the shaded abscissa indicates the normal range for clearance (0.5 l/min to 1.0 l/min).

Figure 1 represents an attempt to integrate the knowledge of the pharmacodynamics and the pharmacokinetics of pethidine for patients with intractable pain by relating the range of MEACs and the range of clearances. In this way dose size and dose frequency may be considered together. The axes are drawn broadly to indicate a 'normal' range for MEAC (0.20 mg/l to 0.40 mg/l) discerned for patients with intractable pain and for clearance (0.50 l/min to 1.0 l/min) (Mather & Meffin, 1978; Edwards *et al.*, 1982). The patients (numbers 1, 2, 6, 9, 11, 12) who were within these ranges, also obtained analgesia from oral and rectal pethidine 200 mg 3 to 6 hourly. It should be remembered that, typically, the oral bioavailability of pethidine is 50–60% while that for rectal pethidine is 80–100% (Glynn & Mather, 1982).

Thus a patient whose MEAC and clearance are to the left in Figure 1 could be treated with smaller doses of pethidine less frequently than the proposed normal (say 3 hourly) dosing schedule. However, the patient with a low MEAC and a normal clearance would need smaller doses at normal frequency, whereas a low MEAC associated with a high clearance would be an indication for normal doses more frequently. A patient with a normal MEAC and low clearance would need normal doses less often whereas, if the MEAC was high, the dose would need to be increased but at a normal frequency. Patients whose results place them on the left of the figure are more likely to have problems associated with overdose of pethidine than other patients.

The patient whose combined results are to the right of Figure 1 (a high MEAC and high clearance) is not

amenable to long term pethidine therapy. Patient number 16 only obtained partial analgesia from the intravenous pethidine, seemingly because of the high clearance (1.54 l/min), so it was not possible to identify her MEAC from the dose regimen used. This patient required a combination of sensory deafferentation of the painful area by intrathecal phenol (Maher, 1955) and other oral narcotics. Patient number 14, whose MEAC was 0.82 mg/l low clearance as 0.36 l/min obtained only such a brief period of analgesia that it was likely narcotic therapy was not the modality of choice. Sensory deafferentation of the painful area with phenol provided satisfactory analgesia. In addition, patients to the right of Figure 1 have more potential for problems associated with overdosing (high MEAC) or for adverse effects due to metabolites (high clearance) (Austin *et al.*, 1981b). It follows therefore that patients whose MEAC and/or clearance place them to the right of Figure 1 are more likely to 'develop' intractable pain because of apparent therapeutic failure and, as a consequence of these pharmacodynamics and pharmacokinetics, be more difficult to treat. This supports the hypothesis that there are sometimes pharmacological reasons for pain 'becoming intractable' in some patients (Glynn, 1979). The clinical pharmacokineticist has an important role in identifying such pharmacological problems.

Patients with intractable pain are not amenable to long term narcotic therapy unless they have a low splanchnic clearance of the agent enabling oral dosing

Figure 2 The relationship between the clearance of pethidine and the duration of analgesia in patients with intractable pain. The patients whose MEAC is equal to or greater than the median (0.25 mg/l) are indicated by ●, the mean $\pm$ s.d. duration of analgesia in these patients was 85 ± 62 minutes or 95 ± 57 min, when patient number 16 was excluded. The patients whose MEAC was less than the median are indicated by ○, the mean $\pm$ s.d. duration of analgesia for these patients was 204 ± 100 min.

or a low MEAC. The relative importance of these two terms for pethidine can be assessed from Figure 2 in which the duration of action is plotted against the clearance. For patients having an MEAC greater or equal to the median value, the duration of action was 95 ± 57 min (mean $\pm$ s.d.) if patient number 16 (partial analgesia only) was excluded or 85 ± 62 min if patient number 16 was assigned a duration of zero. This value should be compared with that for patients having MEAC less than median value. In these patients, the duration of action was 204 ± 100 min. Although clearance was correlated with body weight ($r = 0.66$, $P < 0.001$, $CI = 0.013 \times \text{weight} - 0.09$), it was not important whether duration of action was plotted against total body clearance or weight normalised clearance as duration was totally un-

related to clearance. Hence it would appear that the MEAC is the dominating factor in determining the likelihood of successful therapy with pethidine in patients with intractable pain.

This study identifies an important role for clinical pharmacokinetics in the diagnosis and treatment of patients with intractable pain. In addition it provides pharmacological evidence as to why, in some patients, pain appears to become intractable to conventional techniques of providing analgesia.

The authors would like to thank Sister S. White and Sister K.H.A. Evans for their help in this study, Mr Colin McLean for assaying the pethidine concentrations and Ms Lyda Arman for typing the manuscript.

Reprint requests should be addressed to C.J.G.

References

- AUSTIN, K.L., STAPLETON, J.V. & MATHER, L.E. (1980). Relationships between blood meperidine concentration and analgesic response. *Anesthesiology*, **53**, 460–466.
- AUSTIN, K.L., STAPLETON, J.V. & MATHER, L.E. (1981a). Pethidine clearance during continuous intravenous infusions in post-operative patients. *Br. J. clin. Pharmacol.*, **1**, 25–30.
- AUSTIN, K.L., STAPLETON, J.V. & MATHER, L.E. (1981b). Rate of formation of norpethidine from pethidine. *Br. J. Anaesth.*, **53**, 255–258.
- EDWARDS, D.J., SVENSSON, C.K., VISCO, J.P. & LALKA, D. (1982). Clinical pharmacokinetics of pethidine (meperidine): 1982. *Clin. Pharmacokin.*, **7** (in press).
- GLYNN, C.J. (1979). The pain clinic. *Aust. J. Physiother.*, **25**, 3–7.
- GLYNN C.J., LLOYD, J.W. & FOLKARD, S. (1981). The effect of reported arousal, anxiety, aggression and depression at the diurnal variation of reported pain. *Pain*, Supplement 1: S74.
- GLYNN, C.J. & MATHER, L.E. (1982). Clinical pharmacokinetics applied to patients with intractable pain: Studies with pethidine. *Pain* (in press).
- HUG, C.C. Jr. & MURPHY, M.R. (1979). Fentanyl disposition in cerebrospinal fluid and plasma and its relationship to ventilatory depression in the dog. *Anesthesiology*, **50**, 342–349.
- HUG, C.C. Jr., MURPHY, M.R., RIGEL, E.P. & OLSON, W.A. (1981). Pharmacokinetics of morphine injected intravenously into the anesthetized dog. *Anesthesiology*, **54**, 38–47.
- LITTLEJOHNS, D.W. & VERE, D.W. (1981). The clinical assessment of analgesic drugs. *Br. J. clin. Pharmacol.*, **11**, 319–332.
- MAHER, R.M. (1955). Relief of pain in incurable cancer. *Lancet*, **i**, 18–20.
- MATHER, L.E. & MEFFIN, P. (1978). Clinical pharmacokinetics of pethidine. *Clin. Pharmacokin.*, **3**, 352–368.
- MATHER, L.E. & TUCKER, G.T. (1974). Meperidine and other basic drugs: General method for their determination in plasma. *J. pharm. Sci.*, **63**, 306–307.
- MERSKEY, H., ALBE-FESSARD, D.G., BONICA, J.J., CARMON, A., DUBNER, R., KERR, F.W.L., LINDBLOM, U., MUNFORD, J.M., NATHAN, P.W., NOORDENBOS, W., PAGNI, C.A., RENAER, M.J., STERNBACK, R.A. & SUTHERLAND, S. (1979). Pain terms: A list with definitions and notes on usage. *Pain*, **6**, 249–252.
- STAPLETON, J.V., AUSTIN, K.L. & MATHER, L.E. (1979). A pharmacokinetic approach to post-operative pain: Continuous infusion of pethidine. *Anaesth. Intens. Care*, **7**, 25–32.

(Received April 2, 1982,
accepted May 13, 1982)