Anesthesiology
55:520-526, 1981

Peridural Meperidine in Humans:

Analgetic Response, Pharmacokinetics, and Transmission into CSF

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Effective analgesia resulted from the injection of peridural meperidine in two groups of cancer patients, eight with postoperative pain and eight with intractable pain. Peridural meperidine HCl, 100 mg (n = 8), in 10 ml saline administered to patients following surgery was followed by a median duration of analgesia of 6 hours (range 4–20 hours) over periods ranging from 1–4 days. Peridural meperidine HCl, 30–100 mg (n = 8), in 10 ml saline administered to patients with intractable pain gave a median duration of analgesia of 8 hours (range 4–20 hours) over periods ranging from 1–9 days. There was no obvious tendency towards tolerance. In all patients, the onset of analgesia was within 5 min and was complete within 30 min. This analgesia paralleled the rise in CSF meperidine concentrations following peridural administration. Systemic absorption of peridurally administered meperidine occurred with a half-life of 15–30 min and produced blood concentrations high enough to contribute to analgesia after approximately 20 min in the majority of patients. There was no objective evidence of any neurological change nor sympathetic blockade after peridural meperidine. From this evidence the dorsal horn of the spinal cord may be the major site of action as distinct from the axonal blockade produced by local anesthetics, indicating 'selective' spinal analgesia. (Key words: Analgesics: meperidine. Anesthetic techniques: peridural. Pain: intractable; postoperative. Pharmacokinetics: meperidine.)

THE GATE THEORY OF PAIN[1] focused attention on the importance of the dorsal horn of the spinal cord in the modification of pain transmission. Since then, opiate receptors have been demonstrated in the dorsal horn[2] and it has been shown that the transmission of pain can be blocked at a spinal cord level by intrathecally injected enkephalin,[3] β-endorphin,[4] opiates,[5] serotonin,[6] noradrenaline,[7] and baclofen.[8]

It has been documented that morphine injected via the lumbar subarachnoid space of cancer patients with intractable pain provided analgesia for up to 24 hours.[9] In addition, the injection of morphine into the peridural space of patients with acute and intractable pain resulted in up to 24 hours' analgesia.[10] However, the site of action of the narcotics injected via the peridural space is speculative.

We selected meperidine for study because its physicochemical properties suggest that it would rapidly penetrate the dura[11] and because it is possible to measure accurately and specifically the concentrations of meperidine in blood and CSF.[12] Therefore, we designed a study which asked four questions: 1) Does peridural meperidine provide analgesia and for what duration? 2) Is the site of action at the spinal cord? 3) What is the time course of meperidine concentrations in the blood and CSF and do these correlate with the time course of analgesia? 4) Are there any adverse effects of peridural meperidine? To answer these questions two groups of patients were studied: patients with postoperative pain following surgery for cancer, and patients with intractable pain associated with cancer.

Methods

PATIENT PREPARATION

Informed consent** was obtained from 16 patients with cancer: eight with postoperative pain and eight with intractable pain defined as pain of at least one-month duration and not relieved by conventional techniques†† (table 1). All patients with intractable pain were receiving narcotics for their pain before the study (table 2) but there was no evidence of physical addiction either during or after the study. The dermatomal distribution of the individual patients pain (table 1) was documented by the anesthesiologist before insertion of the peridural catheter and during the study.

Using standard techniques, a Portex® peridural catheter was inserted in each of the patients. This was done before surgery in those patients to be studied postoperatively. The catheter was advanced so that its tip was judged to be over the midpoint of the spinal cord segments

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Received from the Pain Unit, Department of Anaesthesia and Intensive Care, and the Department of Medicine, Flinders Medical Centre, Bedford Park, South Australia 5042. Accepted for publication April 17, 1981. Presented at the first annual meeting of the Australasian Chapter of the International Association for the Study of Pain, Surfers Paradise, May, 1979.

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** This study was approved by the Committee on Clinical Investigation of the Flinders Medical Centre.

†† Conventional technique means that all the diagnostic and therapeutic procedures appropriate for that cancer have been carried out.

TABLE 1. Patient Characteristics and Treatment

Patient Number	Cancer site of Lesion	Dose (mg)	Sex	Age (yr)	Weight (kg)	Dermatomal Distribution of Pain*		Insertion of Peridural Catheter
1	Colon†	100	F	55	52	T5–T12		T11–T12
2	Colon†	100	M	73	65	T5–T12		T11–T12
3	Lung†	100	M	58	51	T2–T12		T8–T9
4	Colon†	100	F	52	62	T5–T12		T4–T5
5	Lung†	100	M	70	65	T2–T12		T8–T9
6	Lung†	100	M	55	41	T2–T10		T8–T9
7	Lung†	100	M	77	65	T2–T10		T8–T9
8	Lung†	100	M	37	68	T2–T10		T8–T9
9	Multiple Myeloma†	30	M	50	80	T5–T12	(bilateral)	T9–T10
10	Rhabdomyosarcoma	30	F	43	44	T12–L3	(unilateral)	T11–T12
11	Lung	30	M	44	88	T7–T8	(unilateral)	T6–T7
12	Lung/Stomach	100	M	66	52	T5–T12	(bilateral)	T11–T12
13	Breast	50	F	54	72	T8	(unilateral)	T9–T10
14	Adrenal‡	50	F	52	44	T5–T12	(bilateral)	T9–T10
15	Renal Cell	100	F	54	90	S1–S5	(unilateral)	T12–L1 T12–L1
16	Adenocarcinoid‡	100	M	53	81	L3–4, 5, S1	(unilateral)	

* Dermatomal distribution of pain was documented by the anesthesiologist before insertion of the peridural catheter and during the study.

† Postoperative group.

‡ Naloxone, 0.4 mg, iv, administered to these patients (see Methods).

responsible for the transmission of that patient's pain (table 1). Peridural meperidine, as requested by the patient, was the only form of analgesia provided during the study. All patients had patent intravenous cannulae and the studies were supervised by the medical staff. The patients were encouraged to be as active as possible in the circumstances.

For patients with postoperative pain, 100 mg meperidine HCl in 10 ml saline was injected via the peridural catheter over 2 min. Patients with intractable pain were injected with 30 mg (n = 3), 50 mg (n = 2), or 100 mg (n = 3) meperidine HCl in 10 ml saline in the same manner. All meperidine solutions were sterilized by autoclaving and were preservative-free.

EXPERIMENTAL DESIGN

The studies were performed in stages on separate days. Stage 1 comprised an intravenous pharmacokinetic study; Stage 2 a peridural pharmacokinetic study; Stage 3 a local anesthetic and placebo study; and Stage 4 sympathetic activity study. No narcotics were administered after midnight before both pharmacokinetic studies.

PHARMACOKINETIC STUDIES

In seven patients (table 3) 100 mg meperidine HCl in 12 ml saline was injected via a peripheral vein over 60 s. Central venous blood was sampled over six hours for the measurement of meperidine (as base) by gas-liquid chromatography.[12] The blood concentration-time relationship after intravenous injection was used to derive the parameters of a two-compartment open model for meperidine.[13] After peridural injection, blood was sampled from a central venous catheter at specific times over a 4- to 6-hour period and the concentrations of meperidine were determined as before. In eight patients CSF was concurrently sampled at 5-min intervals for 45 min via an indwelling needle placed at L3–L4 and which was removed after sampling. From these data the CSF/blood meperidine concentration ratio was determined. The absorption rate of meperidine into the systemic circulation was then calculated from the combined intravenous and peridural data obtained from the same patient in the manner as previously reported for local anaesthetic agents.[14] The relationship between body weight and the areas under the blood and CSF meperidine and concentration-time curves after peridural injection was examined.

EFFECTS OF MEPERIDINE

In those patients studied after both peridural and intravenous administration, the patients were asked to evaluate their pain using a pain score questionnaire,[15] as well as any other symptoms at the time of each blood sampling. Three patients were given 0.4 mg naloxone, IV, to evaluate any antagonism of peridural analgesia (table 1).

After the pharmacokinetic studies, seven patients had injections of 10 ml 0.5 per cent bupivacaine HCl via the catheter to confirm the peridural placement of the catheters (table 3) and six patients were tested for placebo response by injection of 10 ml physiological saline via the catheter. It was considered unethical to give placebo injections to the patients with postoperative pain.

The effect of peridural meperidine on sympathetic

TABLE 2. Analgetic Therapy

Patient Number	Analgetic Therapy before Admission to Study	Analgesia Resulting From Peridural Meperidine (hours)		Number of Days	Total Number of Injections	Post-study Therapy
		Median	Range			
1	——	7	4–20	1	2	Simple nonnarcotic analgesia
2	——	6	5–7	3	6	Simple nonnarcotic analgesia
3	——	6	5–8	2	7	Simple nonnarcotic analgesia
4	——	7	4–20	2	6	Simple nonnarcotic analgesia
5	——	7	5–13	3	6	Simple nonnarcotic analgesia
6	——	13	4–20	4	7	Simple nonnarcotic analgesia
7	——	5	4–7	3	12	Simple nonnarcotic analgesia
8	——	7	4–12	2	5	Simple nonnarcotic analgesia
9	Meperidine, 100 mg, im, 4 hourly PRN for 2 weeks	9	5–15	9	11	Oral and rectal meperidine
10	Morphine, 15 mg, orally, Benorylate, 600 mg, 2 hourly for 4 weeks	8	5–18	4	8	Died
11	Meperidine, 100 mg, im, 4 hourly PRN for 6 weeks	10	6–25	6	13	Oral and rectal meperidine
12	Papaveretum, 15 mg, im, 4 hourly PRN for 3 days	18	10–24	4	3	Bilateral phenol; Splanchnic nerve blockade
13	Morphine, 10 mg, orally, Benorylate, 600 mg, 4 hourly for 1 week	19	19	2	2	Radiotherapy
14	Morphine, 10 mg, orally, Benorylate, 600 mg, 2 hourly for 8 weeks	5	4–7	2	4	Oral and rectal meperidine
15	Morphine, 10 mg, orally, Benorylate, 600 mg, 2 hourly for 12 weeks	5	3–9	7	27	Bilateral phenol; Splanchnic nerve blockade
16	Morphine, 15 mg, im, 2 hourly PRN for 2 days	4	2–9	9	49	Radiotherapy

activity in the feet was assessed before and after peridural injection in five patients (patients 6, 9, 11, 12, 14), by measuring 1) skin temperature with a thermister placed on the dorsum of the foot at the first interspace, 2) sweating on the sole of the foot by a cobalt blue sweat test,[16] 3) skin blood flow by venous occlusion plethysmography,[17] and 4) the ice response of skin blood flow, by venous occlusion plethysmography.[18] These investigations were commenced one-half hour after the peridural injection, and took approximately one hour to complete. In addition, a physician member of the investigation team (JRG) examined five patients (patients 9, 11, 14, 15, 16) neurologically before and after peridural meperidine.

Results

All patients obtained pain relief with peridural meperidine. Generally the onset of analgesia was detectable within five minutes and was complete within 12–30 min. The median duration of pain relief for the eight postoperative patients who received 100 mg meperidine HCl peridurally, was 6 hours (range 4–20 hours) over the study period which varied from one to four days (table 2). The median duration of pain relief for the eight patients with intractable pain who had 30, 50, or 100 mg meperidine HCl peridurally, was 8 hours (range 4–25 hours) during the study period which varied from one to nine days (table 2). During the period of the study, there was no evidence of increased dose requirements. (table 3)

Complete intravenous pharmacokinetic data were available for seven patients and the parameters of a two-compartment open model were derived (table 4). Results for patients 6, 9, and 11 were typical of meperidine pharmacokinetics.[13] While those for patient 12 were quantitatively similar, there was no redistribution phase,

TABLE 3. Mean Duration (hours) between Peridural Injections of Meperidine for Each Day

Patient Number	Days								
	1	2	3	4	5	6	7	8	9
1	12								
2	9	9	14						
3	6	8							
4	6	12							
5	11	8	10						
6	20	14	9	9	*				
7	6	4	8						
8	4	7							
9	6	7	9	13	12	17	10	*	12
10	4	7	18						
11	4	10	14	12	*	12			
12	12	24	24	*					
13	12	18							
14	8	5	4	6	9	6	*		
15	4	*	5						
16	5	2	4	4	4	3	5	*	5

* Indicates the day of peridural bupivacaine study and the placebo injections (except for patient 6 who had postoperative pain).

TABLE 4. Intravenous Pharmacokinetic Data Describing Meperidine Disposition after Intravenous Administration*

Patient Number	Cl† (l/min)	V_C‡ (l)	V_{DSS}§ (l)	$t_{\frac{1}{2}\alpha}$¶ (min)	$t_{\frac{1}{2}\beta}$** (min)
1	0.27	84	153	17	401
6	0.53	91	167	8	224
7††	0.71	15	87	3	103
9	0.87	40	236	2	201
11	0.82	84	221	8	203
12	0.47	173	——	——	255
16	1.54	53	241	1	114

* Dose: 100 mg meperidine HCl injected over 1 min.
† Total body (blood) clearance.
‡ Initial dilution volume.
§ Volume of distribution at steady state equilibirium.
¶ Fast half-life (redistribution phase).
** Slow half-life (elimination phase).
†† Arterial blood was sampled in this patient.

hence the model simplified to a single-compartment system. Low clearance and prolonged slow half-life ($t_{1/2_\beta}$) were noted in patient 1 (hepatic lobectomy), while high clearance and short $t_{1/2_\beta}$ were noted in patient 16 (adenocarcinoid). Arterial blood was sampled from patient 7 and this invalidated comparisons of initial dilution volume and $t_{1/2_\alpha}$ with the other patients. In this patient, clearance was normal but $t^1{}_{/2_\beta}$ was shorter and V_{DSS} was smaller than normal. However, the main use of the intravenous data was to permit calculation of meperidine absorption from the peridural space (fig. 1). The absorption process was exponential (fig. 1) and the logarithm of the fraction of dose unabsorbed at each time was linearly related to time after injection. Absorption half-life ($t_{1/2_{abs}}$) ranged from 15–30 min with a mean of 21 min (SD = 7) (table 5).

Analogies drawn from studies of local anesthetics suggest that both CSF and blood concentrations would be directly proportional to the dose injected while transmission into CSF and blood would follow a similar time course. Thus, observation of the CSF/blood ratio provided a single (dose and time-independent) variable for comparative studies not obtained in either CSF or blood concentrations. Analgesia was related to CSF concentrations (table 6 and fig. 2) in that patients having a high CSF/blood concentration ratio also had complete analgesia (table 5). One patient (patient 7) who had a lower ratio than the others also had arterial blood sampled. This, in part, would have artificially lowered this ratio several-fold. The rapid rise in CSF meperidine concentration in the first five minutes coincided with the onset of analgesia (table 6, fig. 2 and 3). For the majority of patients receiving 100-mg doses meperidine blood concentrations following peridural adminstration reached the range (0.2–0.7 μg/ml) associated with analgesia after iv administration in this group of patients within 20 min

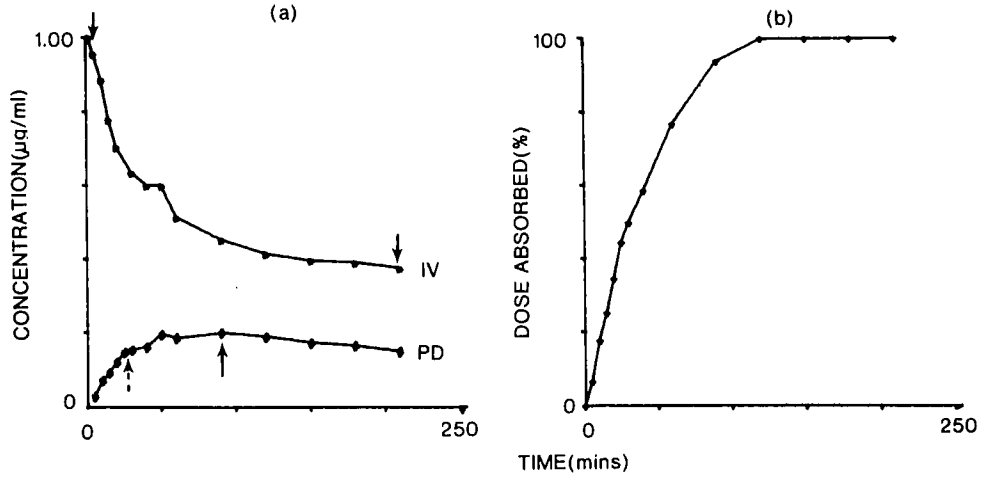

FIG. 1. *A*. Blood concentration-time profiles after intravenous (iv) and peridural (PD) administration of 100 and 50 mg, meperidine HCl, respectively. ↓ indicates onset and regression of analgesia for iv. ↑ and ↑ indicate onset of partial and complete analgesia for PD. Data for Patient 1. *B*. Calculated per cent of dose absorbed with time.

TABLE 5. Half-Life of Meperidine Absorption from Peridural Space, CSF Blood Ratio and Quality of Analgesia after Peridural Administration of Meperidine

Patient Number	$T_{½_{abs}}$ (min)	CSF/Blood Ratio*	Quality of Analgesia
1	28	——	——
3	——	182 ± 100	Complete
5	——	9 ± 7	Parital
6	17	——	——
7†	20	0.9 ± 0.1	Poor
9	15	130 ± 24	Complete
11	15	——	——
12	30	330 ± 130	Complete
14	——	60 ± 25	Complete
15	——	7 ± 6	Poor
16	——	16 ± 2	Partial

* Means ± SD of five determinations sampled between 15–40 min.
† Arterial blood was sampled in this patient.

(table 6). However, an "analgetic meperidine blood concentration" specifically determined after iv injection was not achieved at all during the study period in two of the seven patients (patients 1, 9). There was no significant correlation found between body weight (kg) and area under the blood or CSF concentration-time curves after peridural injection of meperidine.

Peridural meperidine injection did not produce sympathetic blockade in the feet of any of the five patients studied. This was deduced from the absence of change in 1) plantar sweating, 2) skin temperature, 3) skin blood flow, and 4) the ice response of skin blood flow following peridural meperidine injection. All results for these tests were within the normal range for this laboratory except for a significant increase in skin blood flow in one patient (patient 11) which were not associated with any other change in sympathetic activity. Blood pressure decreased significantly (mean 20 torr) with each peridural meperidine injection in the patients with postoperative pain but not those with intractable pain. After peridural meperidine there were no neurological changes found in any of the five patients who had a complete neurological assessment. Placebo injections administered to six patients with intractable pain produced no analgesia. Three patients who were given 0.4 mg naloxone intravenously had incomplete reversal of analgesia after 30 min. There was no clinical reason to cease peridural meperidine in any of the 16 patients studied; particularly, there was no evidence of respiratory depression in any patient. Indeed, there was a distinct absence of the side effects commonly associated with other modes of administration of narcotics, *e.g.*, nausea, vomiting, constipation, and pruritis. A total of 150 peridural meperidine injections were administered over periods of up to nine days (table 2) without any evidence of tolerance (table 3).

Discussion

These results confirm that peridural meperidine provides analgesia, with a duration of approximately two to three times that expected from the same dose given intramuscularly.[19] The difference in analgetic duration between postoperative and intractable pain is not unexpected. It is notable that 30 or 50 mg meperidine given

TABLE 6. CSF and Blood Concentrations of Meperidine (μg/ml, base)

Patient Number		Time (min) 0	5	10	15	20	25	30	35	40	45	AUC‡
3	CSF	0	0.52*	6.6†	11.7	15.3	15.4	17.6	18.9	16.3	19.4	558.5
	Blood	0	0.005	0.02	0.04	0.09	0.17	0.23	0.21	0.24	0.22	5.6
5	CSF	1.50	——	1.62*	1.73	1.92*†	8.4	5.7	6.2	12.8	10.0	220.6
	Blood	0.25	0.32	0.42	0.42	0.52	0.45	0.54	0.47	0.48	0.48	19.9
7	CSF	0.24	0.25*	0.42†	0.55	0.56	0.52	0.55	0.54	0.45	0.39	20.8
	Blood	0.27	0.54	0.63	0.59	0.97	0.53	0.57	0.50	0.43	0.42	24.0
9	CSF	0	0.05*†	9.25	13.0	13.0	16.3	15.3	—	—	—	301.3
	Blood	0	0.04	0.08	0.10	0.13	0.11	0.10	—	—	—	2.6
12	CSF	0.33	9.2*†	43.5	95.3	136	131	162	185	248	257	5693.3
	Blood	0.04	0.11	0.24	0.25	0.27	0.60	0.44	0.38	0.32	0.27	13.8
14	CSF	2.9	30.3*†	36.1	38.6	32.7	15.9	22.1	14.2	10.9	7.6	1032.8
	Blood	0.34	6.78	0.72	0.43	0.43	0.60	0.42	0.36	0.83	2.0	28.7
15	CSF	0	——*	0.11	1.58	2.03	2.45	—	—	—	—	24.2
	Blood	0	0.25	0.31	0.28	0.28	0.17	—	—	—	—	6.0
16	CSF	3.5	5.9*	13.0	12.1†	9.9	14.5	—	11.1	15.4	13.7	453.5
	Blood	0.53	0.66	0.80	0.79	0.78	0.79	0.70	0.60	0.69	0.72	32.2

The results at 0 time indicate multiple doses.
* Indicate onset of analgesia.
† Indicates complete analgesia.
‡ Area under curve (trapezoidal rule).

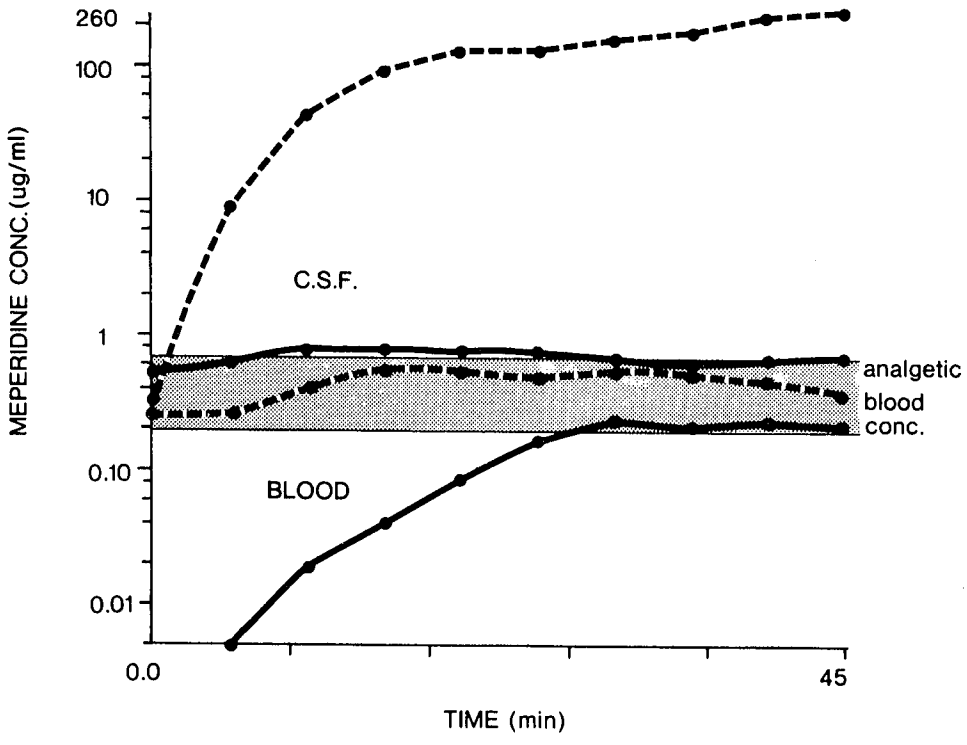

FIG. 2. This figure shows the range of CSF meperidine (---) and blood meperidine (O —— O) concentrations for the eight patients studied after peridural injection. The shaded area is the range of blood meperidine concentrations associated with analgesia found in the seven patients who were studied after intravenous meperidine.

peridurally to the five patients with intractable pain produced a mean duration comparable to 100 mg meperidine given to the postoperative pain patients. These results support those of Behar *et al.*[10] who reported that patients with acute pain achieved only 50 per cent analgesia from 2 mg peridural morphine, whereas patients with chronic pain had complete analgesia from the same dose.

The peridural meperidine was not associated with the commonly reported side effects of the drug. All postoperative patients were mobilized on the second day and maintained a postoperative routine appropriate to their surgery. Apart from two intractable pain patients (patients 10 and 16), who were confined to bed by their disease, all the other patients in the group were mobile. Tolerance did not appear to be a significant problem in the five patients who received peridural meperidine for more than four days (table 3). Four patients with intractable pain (patients 12, 13, 14, 16) whose narcotic medication was withdrawn after successful treatment of their pain (table 2), showed no symptoms or signs of withdrawal. These findings have been supported recently by others.[20]

Respiratory depression was not observed in any patient in our study, but respiratory depression has been reported in two patients following 100 mg peridural meperidine in the immediate postoperative period.[21] As both of these patients received diamorphine premedication, it is possible that there was an additive effect of the two opiates on the respiratory center. Others have reported respiratory depression following intrathecal morphine.[22] Thus, care must be taken with the peridural and intrathecal administration of opiates until more is known about their blood and CSF pharmacokinetics. The absorption half-life of peridurally administered meperidine is similar to that of lidocaine.[23] This is not surprising since the two drugs have similar physicochemical properties. Lidocaine absorption, however, is biphasic and also has a slower component having a half-life of 3 h. This was not seen with meperidine but possibly because the sampling duration was insufficient.

Our results suggest that the action of peridural meperidine is at the dorsal horn of spinal cord rather than the brain. The evidence in favor of this concept is: 1) the rise in CSF meperidine concentrations coincides with the onset of analgesia but the blood concentration is less than previously reported analgetic blood concentrations.[15] (In addition, the duration of analgesia was considerably longer than from the same dose given intramuscularly[19]); 2) complete analgesia was associated with high CSF/blood ratios of meperidine whereas incomplete analgesia was associated with low ratios; 3) there was an absence of overt signs of sensory or motor blockade in any patient; 4) naloxone reversal of analgesia in the three patients studied took 30 min and was incomplete; and 5) the lack of objective evidence of sympathetic blockade in conjunction with the absence of neurological changes in the five patients studied, suggested that the 1 per cent meperidine HCl solution injected had no detectable local anaesthetic effect on the peripheral nerves in the peridural space. This implies that the major action is at the

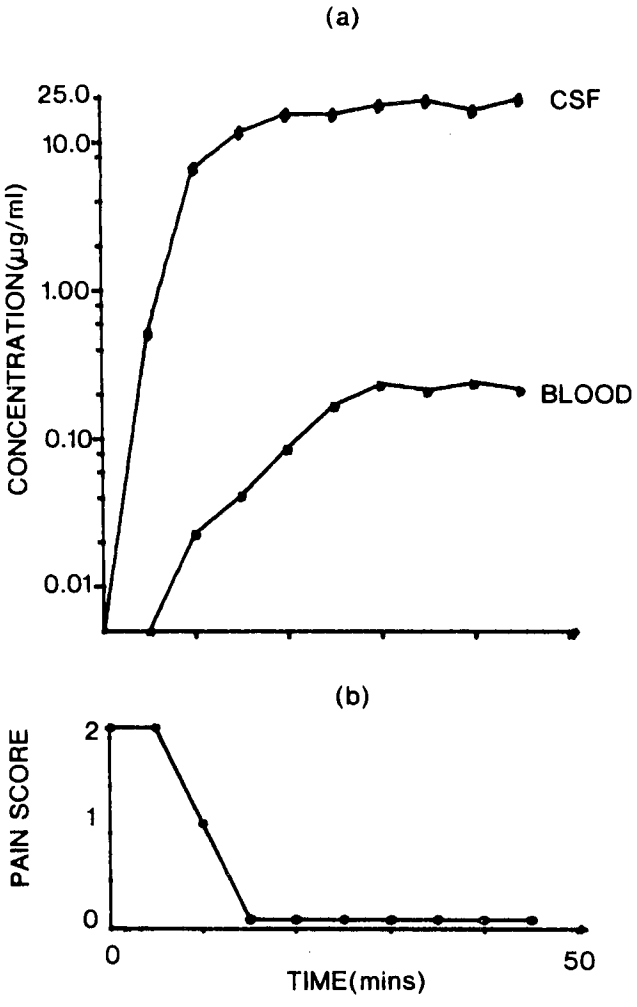

FIG. 3. *A.* Blood and CSF concentration (log scale) after peridural administration of 100 mg meperidine HCl. Data for Patient 12. *B.* Pain score: 2 = no analgesia; 1 = partial; 0 = complete.

spinal cord as distinct from the axonal blockade produced by local anesthetics. However, a central contribution to the analgesia cannot be excluded because of the meperidine blood concentrations achieved.

In conclusion, peridural meperidine relieved intractable pain and postoperative pain in patients with cancer. The present data suggest that peridural meperidine has its major analgetic effect via the spinal cord. The absence of neurologic changes apart from pain relief suggests a selective spinal analgesia.[24] However, vascular absorption may contribute at least partially to analgesia and may combine with meperidine in the CNS to produce respiratory depression.

The authors acknowledge the technical skills of Mr. C. McLean and Dr. R. W. Basedow.

References

1. Melzack R, Wall PD: Pain mechanisms: A new theory. Science 150:971–979, 1965
2. Atweh SF, Kuhar MJ: Autoradiographic localization of opiate receptors in rat brain, spinal cord and lower medulla. Brain Res 123:53–67, 1977
3. Yaksh TL, Huang SP, Rudy TA: The direct and specific opiate-like effect of Met[5] enkephalin and analogues on the spinal cord. Neuroscience 2:593–596, 1977
4. Oyama T, Jin T, Yamaya R, et al.: Profound analgesic effects of β-endorphine in man. Lancet 1:122–124, 1980
5. Yaksh TL, Pert A: Analgesia mediated by a direct spinal action of narcotics. Science 192:1357–1358, 1976
6. Wang JK: Antinociceptive effect of intrathecally administered serotonin. ANESTHESIOLOGY 47:269–271, 1977
7. Reddy SVR, Yaksh TL: Spinal noradrenergic terminal system mediates antiociception. Brain Res 189:391–401, 1980
8. Wilson PR, Yaksh T: Baclofen is antinociceptive in the spinal intrathecal space of animals. Eur J Pharmacol 51:323–330, 1978
9. Wang JK, Nauss LA, Thomas JE: Pain relief by intrathecally applied morphine in man. ANESTHESIOLOGY 50:149–151, 1979
10. Behar M, Magora F, Olshwang D, et al: Epidural morphine in the treatment of pain. Lancet 1:527–529, 1979
11. Herz A, Teschemacher HJ: Activities and sites of antinociceptive action of morphine-like analgesics. Adv Drug Res 6:79–119, 1971
12. Mather LE, Tucker GT: Meperidine and other basic drugs: General method for their determination in plasma. J Pharm Sci 63:306–307, 1974
13. Mather LE, Meffin PJ: Clinical pharmacokinetics of pethidine. Clin Pharmacokinet I 3:352–368, 1979
14. Tucker GT, Mather LE: Pharmacokinetics of local anaesthetic agents. BR J Anaesth 47:213–224, 1975
15. Stapleton JV, Austin KL, Mather LE: A pharmacokinetic approach to postoperative pain: Continuous infusion of pethidine. Anaesth Intensive Care 7:25–32, 1979
16. Cousins MJ, Reeve TS, Glynn CJ, et al: Neurolytic lumbar sympathetic blockade: Duration of denervation and relief of rest pain. Anaesth Intensive Care 7:121–135, 1979
17. Greenfield ADM: A simple water-filled plethysmograph for hand or forearm with temperature control. J Physiol (Lond) 123:62–64P, 1954
18. Jamieson GG, Ludbrook J, Wilson A: The response of hand blood flow to distant ice application. Aust J Exp Biol Med Sci 49:145–152, 1971
19. Austin KL, Stapleton JV, Mather LE: Multiple intramuscular injections: A major source of variability in analgesic response to meperidine. Pain 6:47–62, 1980
20. Zenz M, Schappler-Scheele B, Neuhaus R, et al: Long-term peridual morphine analgesia in cancer pain. Lancet, 1:91, 1981
21. Scott DB, McClure J: Selective epidural analgesia. Lancet 1:1410–1411, 1979
22. Glynn CJ, Mather LE, Cousins MJ, et al: Spinal narcotics and respiratory depression. Lancet 2:356–357, 1979
23. Tucker GT, Mather LE: Clinical pharmacokinetics of local anesthetics. Clin Pharmacokinet 4:241–278, 1979
24. Cousins MJ, Mather LE, Glynn CJ, et al: Selective Spinal Analgesia. Lancet 1:1141–1142, 1979