

Biphasic Depression of Ventilatory Responses to CO₂ Following Epidural Morphine

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The authors examined the duration of effects of lumbar epidural morphine (0.1 mg/kg) on control of ventilation (CO₂ response), pain relief, segmental analgesia (loss of pain in response to a painful stimulus) and loss of temperature discrimination, and plasma morphine concentrations in seven patients with chronic low back pain at 1, 2, 4, 8, 12, and 24 h postinjection. Maximal depression of the slope of the minute ventilation response to CO₂ occurred at one to two hours postinjection and expressed as per cent reduction from control (measured day before epidural morphine injection) (\pm SEM) was -35 ± 7 ($P < 0.01$); the tidal volume (V_T) and average inspiratory flow (\bar{V}_I) responses were displaced to the right (V_T or \bar{V}_I at PETCO₂55), -29 ± 3 ($P < 0.01$) and $-37 \pm 4\%$ ($P < 0.001$), respectively. At eight hours postinjection, the minute ventilation and average inspiratory flow were displaced to the right, and as per cent reduction from control at PETCO₂55 were -52 ± 19 ($P < 0.05$) and -36 ± 13 ($P < 0.05$), respectively. At 4, 12, and 24 h postinjection, the CO₂ responses were not significantly different from control. The segmental level of analgesia and loss of temperature discrimination, which was highest at eight hours postinjection, rose in different patients to high thoracic, cervical, or trigeminal nerve segments. Plasma concentrations of unconjugated morphine were highest at 0.25 h postinjection and declined polyexponentially with a $t_{1/2\beta}$ of 2.38 ± 0.23 h. The authors speculate that epidural morphine causes biphasic depression of control of ventilation by two mechanisms: 1) an early depression resulting from absorption into the epidural veins and circulatory redistribution to the brain, and 2) a late phase associated with a rise in the segmental level of analgesia, which is

the result of cephalad movement of morphine in the CSF. The rise in segmental analgesia and loss of temperature discrimination therefore may be an essential clinical sign of impending late depression of control of ventilation. (Key words: Analgesics: morphine. Anesthetic techniques: epidural morphine. Pain. Pharmacokinetics: morphine. Ventilation: carbon dioxide response.)

THE EFFECTIVE MANAGEMENT of acute and chronic severe pain remains one of the major challenges in medicine. Systemic administration of opiates alters the sensorium, depresses ventilation, and results in drug dependence. Regional analgesia produced by epidural administration of a local anesthetic causes autonomic blockade, impairs neuromotor function, and the continuous administration and monitoring are logistically difficult. Therefore, lumbar epidural or subarachnoid morphine analgesia which is selective, prolonged, and was presumed to be segmental, aroused considerable interest.^{1,2} Although large series with low incidences of complications have been reported,³ case reports of severe depression of ventilation 2–12 h following administration of epidural or subarachnoid morphine and other opiates resulted in concern about the safety of subarachnoid and epidural morphine. The majority of episodes of severe depression of ventilation followed subarachnoid morphine, but there are case reports of depression of ventilation following epidural morphine.^{4–7}

We propose that the early and continuing pain relief and the early and late depression of control of ventilation following lumbar epidural morphine are the result of different processes: 1) early pain relief and depression of ventilation are the result of rapid absorption of morphine into the epidural veins and circulatory redistribution to the brain; 2) continuing pain relief is the result of morphine diffusing through the lumbar dura and subarachnoid membranes into the cerebrospinal fluid (CSF) and to the dorsal horns of the spinal cord; and 3) late respiratory depression is the result of cephalad movement of morphine within the CSF to cisterna magna where at 4–12 h postinjection the concentrations may be sufficient to depress respiratory control.

Therefore, the goals of our study were to examine the time course of the effects of lumbar epidural morphine on pain relief, mood, segmental level of analgesia and impaired temperature discrimination, neuromotor function of the respiratory system, minute ventilation and its component responses to CO₂ and plasma mor-

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phine concentration for 24 h postinjection. Our experimental model consisted of patients with chronic severe low back pain who were attending the pain clinic. The advantages of this group of patients were that their pain was relatively stable and the postinjection period was not complicated by an evolving postoperative course.

Materials and Methods

SUBJECTS

The effects of lumbar epidural morphine on the minute ventilation and its component responses to CO₂ (rebreathing method), vital capacity, heart rate and blood pressure, pain relief, segmental level of analgesia and temperature sensation, and plasma morphine concentrations were examined in seven patients (five men and two women) with chronic low back pain who were attending the Pain Clinic of the North Carolina Memorial Hospital. Their mean age, height, weight and vital capacity (\pm SD) were 39 ± 12 years, 171 ± 9 cm, 78 ± 17 kg, and 3.8 ± 0.7 liters ($91 \pm 14\%$ predicted), respectively. These patients received one epidural injection of morphine during their program of rehabilitation. Except for low back pain the patients were in their normal state of health and did not have severe organ system disease, history of drug addiction, serious psychiatric disorder, bleeding diathesis, or back infection. The protocol was approved by the Human Rights Committee of the School of Medicine and informed consent for the epidural morphine injection and the experimental protocol were obtained from each patient.

PROCEDURE FOR ADMINISTRATION OF EPIDURAL MORPHINE

All patients were admitted to the Clinical Research Unit of the School of Medicine within the North Carolina Memorial Hospital the day prior to injection of morphine sulfate, and were allowed no oral intake for six hours prior to the epidural injection. With the patient in the lateral decubitus or sitting position epidural morphine was administered via an epidural needle (18-gauge, 9-cm Hustead or Crawford epidural needle) which was inserted into the 3–4 or 4–5 lumbar interspace. After identification of the epidural space by "loss of resistance" and absence of cerebrospinal fluid or blood, morphine sulfate (0.1 mg/kg) was injected into the epidural space. The morphine sulfate preparation was preservative-free (A. H. Robins, Richmond, Virginia). The composition per milliliter was 0.5 mg morphine sulfate, 9.0 mg sodium chloride, and water for injection to 1 ml. The mean dose (\pm SD) administered was 7.9 ± 1.6 mg in a volume of 16.0 ± 3.0 ml. During the first hour postinjection with the patient in the semi-

recumbent position, the blood pressure and heart rate were measured every 10 min and hourly from 1 to 24 h using the oscillometric principle (Biochem International, Milwaukee, Wisconsin). Twenty-four hours postinjection (after completion of the studies) the patients were discharged from the Clinical Research Unit. The patients were instructed verbally and in writing not to take any non-prescribed drugs, and to avoid alcohol or driving for 24 h following discharge. They were accompanied home by a responsible adult.

PAIN RELIEF, ANALGESIA AND MOOD RESPONSE TO EPIDURAL MORPHINE

The afternoon prior to injection and at 1, 2, 4, 8, 12, and 24 h postinjection, the severity of pain, mood, segmental level of analgesia (loss of painful sensation in response to a painful stimulus), temperature discrimination, touch, reflex, and motor functions were examined. The patients were asked to grade their chronic pain on a categorical scale of intensity which was no pain = 0; mild pain = 1; moderate pain = 2; and severe pain = 3. Severe pain prevented the patients from performing their normal occupation. The mean duration (\pm SD) of their pain was 4.4 ± 5.8 years and the average severity was 2.6 ± 0.5 (range 2–3). Evaluation of pain relief included latency of onset, quality, and duration. The quality of pain relief also was evaluated on a categorical scale of worse = -1; no change = 0; mild improvement = 1; moderate improvement = 2; and complete relief = 3. The mood evaluation was based on the method of Kaiko and consisted of a series of 15 contrasting word or phrase pairs: "feeling of heaviness/bouyant;" "I feel sociable/I want to be alone."⁸ Each pair was separated by the number -3, -2, -1, 0, 1, 2, 3, and the patients were asked to estimate the direction and value of the mood for each pair. The segmental level of loss of painful sensation was determined as the level at which there was an increased threshold to pain ("sharp" experience). The increased threshold was measured bilaterally over ten regions of the limbs, trunk, and face from the pressure gauge of a spring loaded sharp instrument (Tension Dynamometer Dial Gauge, Jonard Inc., Tukahoe, New York). Heat (45° C) and cold (ice) stimuli were applied on similar segments in random order and the patient was asked to identify the stimulus as touch, cool, cold, warm, or hot. Loss of temperature discrimination was identified as a response of touch.

RESPIRATORY MEASUREMENTS

Respiratory measurements were performed the afternoon prior to the morphine injection (control) and at 1, 2, 4, 8, 12, and 24 h postinjection. All studies were

performed with the patients in the sitting position. The patients were at least two hours postprandial and were requested to empty their urinary bladder prior to each study. The patients also were requested to avoid alcohol, smoking, or caffeine-containing beverages prior to and during the study. The vital capacity (VC) and forced expiratory volume in one second (FEV_1) were measured on a nine-liter lightweight Godart spirometer (Bilthoven, Holland). Control values were expressed in liters, BTPS, and as percentage predicted,⁹ and the postinjection values were expressed in liters, BTPS, and per cent of control.

The minute ventilation, its components, and heart rate responses to CO_2 were measured by the Read rebreathing method.^{10,11} The patients rebreathed CO_2 in oxygen from a rebreathing bag (meterological balloon) which contained initially six liters of 7% CO_2 in oxygen, for a period of four minutes. We measured airflow by pneumotachography (Fleisch 2, Dynasciences, New York; Validyne, Northridge, California), airway pressure (MP 45 Validyne), and obtained tidal volumes by electronic integration of the airflow signal. The CO_2 and O_2 in the respired gases were measured continuously using a Perkin-Elmer Respiratory/Anesthesia mass spectrometer (Pomona, California). All of the above variables and the ECG (lead II) were recorded continuously on a Honeywell 1912 Visicorder. The resistance of the breathing circuit was $0.8 \text{ cmH}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}^{-1}$ at an average inspiratory flow of $2 \text{ l} \cdot \text{s}^{-1}$. Each control study was preceded by a rebreathing test maneuver of four minutes designed to familiarize the patient with the experience of rebreathing CO_2 .

After the first 20 s and at 20-s intervals the PET_{CO_2} , tidal volume (V_T), minute ventilation (\dot{V}_I), average inspiratory flow (\bar{V}_I), respiratory time cycle (T_T) and its components inspiratory (T_I) and expiratory time (T_E), breathing frequency, and heart rate were calculated. All volumes and flows were corrected to BTPS. For each rebreathing test the relationships between PET_{CO_2} and the respiratory variables and heart rate were determined by least-squares linear regression analysis (HP9845B). We examined both the slope and the position (y at PET_{CO_2} 55) of the responses to CO_2 and partitioned the minute ventilation response into its components as listed above. The mechanical transformation of the respiratory drive or rate of rise of the neural efferent signal is the average inspiratory flow, \bar{V}_I , and is obtained by dividing V_T by T_I .¹² In the absence of changes in lung volumes or the mechanical properties of the respiratory system any change in the \bar{V}_I in response to CO_2 is equivalent to a change in respiratory neural drive. The tidal volume is therefore dependent on both the \bar{V}_I or drive and the T_I component of the respiratory time cycle.¹² The respiratory time cycle

which was obtained from the flow signal was partitioned into inspiratory and expiratory time.

PLASMA MORPHINE ANALYSIS

Venous blood was obtained the afternoon prior to injection (control), and at 15, 30, 45, and 60 min, and 2, 4, 8, 12, and 24 h postinjection. Blood samples were collected into EDTA-containing Vacutainers® (Becton Dickinson Co., Rutherford, New Jersey), mixed, and centrifuged at 4° C. Plasma was harvested and stored frozen (−15° C) until analyzed. Unconjugated morphine plasma concentrations were determined by a sensitive and specific radioimmunoassay procedure as described previously.^{13,14} Total (conjugated plus unconjugated) morphine plasma concentrations were determined by radioimmunoassay after enzyme hydrolysis. Patient plasma (0.1 ml) was incubated with Glusulase® (Endo Laboratories, Garden City, New York; 4000 U β -glucuronidase, 700 U sulfatase in 0.025 ml) and 0.2 M sodium acetate buffer, pH 5.5 (0.1 ml) at 37° C overnight. Morphine standard solutions (0.78–100 ng/ml) and controls (10, 100, and 1,000 ng/ml) and a sample of morphine-3-glucuronide (Applied Science Laboratories, State College, Pennsylvania; 1,000 ng/ml), prepared in blank human plasma were treated similarly with enzyme. Radioimmunoassay of hydrolyzed samples were performed as described above, except that 0.1 ml of patient plasma and drug standards were replaced by 0.025 ml of hydrolyzed samples, suitably diluted with enzyme-treated blank human plasma into the assay range.

A standard curve was devised by linear least-squares analysis of a logit-log transformation of the assay data. The model-independent pharmacokinetic parameters, maximum concentration (C_{max}) and time at which maximum concentration occurred (t_{max}), were obtained directly from individual plasma concentration-time data, and the area under the curve (AUC) values for the 0 to 24-h period were calculated by the trapezoidal rule.¹⁵ The terminal half-life ($t_{1/2}$) was calculated by least-squares linear regression of the log plasma concentration-time data for the terminal phase of morphine disposition. The 24-h data were omitted from the analysis because of the absence of additional data from the 12- to 24-h period, and because their exclusion produced only small changes in AUC values.

STATISTICAL ANALYSIS

Standard statistical procedures were used which included calculation of mean, SD, or SEM. The relationships between PET_{CO_2} and the respiratory and heart rate variables were determined by least-squares linear regression analysis. The responses to CO_2 were ex-

pressed as the slope \pm SE, the position as the dependent variable at $PET_{CO_2}55 \pm SE$ and the correlation coefficient. For each patient comparisons between each control and postinjection responses to CO_2 , e.g., the minute ventilation response to CO_2 , the slope and total regressions were compared by analysis of their variance and an F test. A statistically significant difference in the total regression in the absence of a significant change in slope was regarded as equivalent to a displacement of the response to CO_2 . For the group of patients, each set of postinjection variables were compared with the control values for the same patients and equal sample sizes using Tukey's procedure and statistical significance of difference from control was regarded as $P < 0.05$.¹⁶

Results

The mean control slopes and positions of the minute ventilation, and its component responses to CO_2 in the chronic pain patients are in table 1. The coefficients of the variation of the slopes of the tidal volume (68%) and average inspiratory flow (57%) responses were large; normalization of the tidal volume response to the vital capacity did not reduce the variation in slope or position. The minute ventilation, tidal volume, and average inspiratory flow responses were linear in all except one patient in whom the tidal volume response flattened at 45% of the vital capacity. The mean slope (\pm SD) of the frequency response to CO_2 was 0.74 ± 0.59 breaths \cdot min⁻¹ \cdot mmHg⁻¹ and the breathing frequency at $PET_{CO_2}55$ was 20.0 ± 5.5 breaths/min. The heart rate responses to CO_2 were variable and only three of the seven patients increased their heart rate in response to CO_2 . The control blood pressures were systolic and diastolic, 132 ± 7 and 86 ± 8 mmHg, respectively, and the heart rate was 94 ± 16 beats/min.

**ANALGESIC, NEUROLOGIC AND HEMODYNAMIC
RESPONSES TO EPIDURAL MORPHINE**

Following epidural injection of morphine the average onset of pain relief was 23.6 ± 3.1 min and in all except one patient moderate or complete pain relief was achieved within one hour. In all except one patient in whom the pain relief lasted 12 h the relief exceeded 24 h. The time course of mood change was characterized by a peak at one to two hours and was statistically different from control ($P < 0.01$); subsequent mood levels were not significantly different from control. In all except two patients there was a linear rise with time in the segmental level of analgesia and loss of temperature discrimination. In the majority these levels were highest at eight hours postinjection and all receded at 12 h. The highest segmental levels of analgesia (except in the patient described below) were upper thoracic and cervical

TABLE 1. Effect of Epidural Morphine (0.1 mg/kg) on the Minute Ventilation, Tidal Volume, and Average Inspiratory Flow Responses to CO_2 (Rebreathing Method) in Patients with Chronic Low Back Pain

	Control		1 Hour Postinjection		2 Hours Postinjection		4 Hours Postinjection		8 Hours Postinjection		12 Hours Postinjection		24 Hours Postinjection	
	Slope	y at $PET_{CO_2}55$	Slope	y at $PET_{CO_2}55$	Slope	y at $PET_{CO_2}55$	Slope	y at $PET_{CO_2}55$	Slope	y at $PET_{CO_2}55$	Slope	y at $PET_{CO_2}55$	Slope	y at $PET_{CO_2}55$
Minute ventilation: Slope, $l \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$; position, l/min														
MEAN	3.18	34.4	2.46	23.6	2.26	22.7	2.84	34.2	3.28	21.4	3.27	33.9	3.30	36.7
SEM	± 0.59	± 4.7	± 0.54	± 4.5	± 0.36	± 2.4	± 0.70	± 7.9	± 0.65	± 10.0	± 0.64	± 8.1	± 0.48	± 7.0
Tidal volume: Slope, l/mmHg; position, l														
MEAN	0.118	1.78	0.095	1.38	0.090	1.28	0.111	1.68	0.124	1.36	0.113	1.86	0.116	1.76
SEM	± 0.030	± 0.32	± 0.028	± 0.25	± 0.013	± 0.18	± 0.029	± 0.41	± 0.032	± 0.47	± 0.019	± 0.37	± 0.022	± 0.34
Average inspiratory flow: Slope, $l \cdot s^{-1} \cdot \text{mmHg}^{-1}$; position, l/s														
MEAN	0.11	1.26	0.09	0.94	0.09	0.90	0.11	1.32	0.11	0.90	0.11	1.33	0.13	1.35
SEM	± 0.02	± 0.18	± 0.02	± 0.17	± 0.01	± 0.08	± 0.03	± 0.03	± 0.02	± 0.30	± 0.02	± 0.30	± 0.02	± 0.27
n	7	7	7	7	7	7	5	5	5	5	5	5	6	6

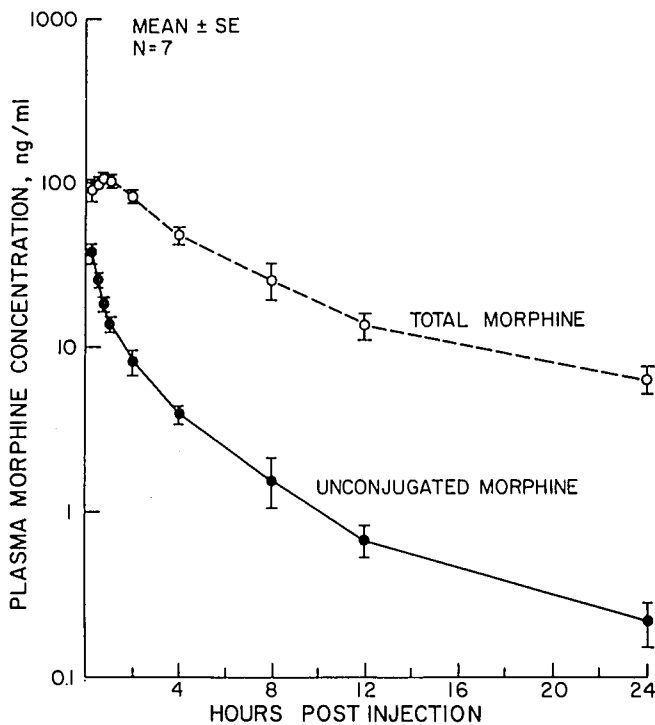


FIG. 1. Plasma concentration-time profiles for unconjugated (●—●) and total (unconjugated plus conjugated; ○---○) morphine in patients receiving epidural morphine (0.1 mg/kg). Values are means \pm SE for seven patients. Unconjugated morphine was determined by direct radioimmunoassay, and total morphine by radioimmunoassay after enzyme hydrolysis as described in the Materials and Methods.

(four patients). In two patients the segmental level of analgesia remained at lumbar 1 and thoracic 11. In one patient three hours after injection a coughing episode was followed by a rapid rise in the segmental level of analgesia, and at four hours included the maxillary and mandibular divisions of the trigeminal nerve. This was associated with severe depression of ventilation which was reversed by naloxone. The depression of ventilation recurred at eight hours and was again reversed by naloxone. The depression of ventilation was associated with drowsiness but not with hypotension. In all patients alterations in the sensation of touch, tendon reflexes, motor control, and coordination were absent.

The side effects included pruritus which was nonsegmental, mainly on the trunk and was maximal at 4–12 h (three patients); urinary retention as a result of loss of sensation of a full bladder (none required catheterization) (three patients); headache (three patients) and nausea and/or vomiting which was present at 4, 8, and 12 h postinjection (three patients). Inability to measure the ventilatory responses to CO_2 in all patients at all of the times together with the patient who developed respiratory depression accounted for the missing data at 4, 8, and 12 h postinjection.

Neither the blood pressure nor the heart rate at 1, 2, 4, 8, 12, or 24 h were significantly different from the control values. In the majority of patients during the first 30 min following epidural administration of morphine there was mild orthostatic hypotension. There was no orthostatic hypotension during any of the respiratory function tests.

There was no significant change in either the VC or the FEV₁ following the epidural administration of morphine.

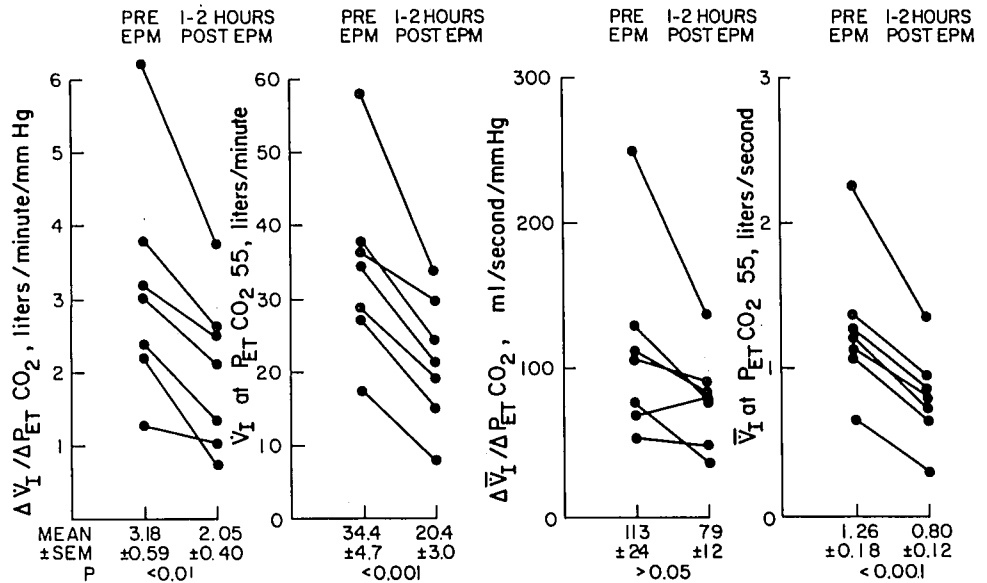
MORPHINE PLASMA CONCENTRATIONS

Mean unconjugated and conjugated morphine plasma concentrations following lumbar epidural morphine are shown in figure 1. Unconjugated morphine plasma concentrations peaked at 0.25 h in all except one patient in whom the peak plasma concentration was at 0.50 h. The mean plasma concentrations of unconjugated morphine declined polyexponentially. The terminal half-life, calculated by linear regression analysis of the terminal disposition phase, was 2.38 ± 0.23 h (seven patients). Throughout the period of observation the concentrations of morphine glucuronide exceeded the concentrations of unconjugated morphine. Even at 0.25 h postinjection plasma concentrations of total morphine were 1.7- to 2.8-fold higher than those of unconjugated morphine, and the relative percentage of conjugated morphine continued to increase with time. The mean concentration-time profiles (fig. 1) indicate that total morphine plasma concentrations peaked later than did unconjugated morphine levels. The mean area under the total morphine plasma concentration-time curve for these subjects (670 ± 51 ng \cdot ml⁻¹ \cdot h) was approximately tenfold greater than that for unconjugated morphine (68.9 ± 6.5 ng \cdot ml⁻¹ \cdot h).

EFFECT OF EPIDURAL MORPHINE ON THE VENTILATORY RESPONSES TO CO_2

At one and two hours postinjection the slopes of the minute ventilation and its component responses were significantly reduced from control (table 1, figs. 2 and 3). Expressed as the per cent reduction (\pm SE) from control the maximal reductions at one or two hours were minute ventilation $\Delta\dot{V}_1/\Delta\text{PET}_{\text{CO}_2}$ $-35 \pm 7\%$ ($P < 0.01$), \dot{V}_1 at $\text{PET}_{\text{CO}_2}55$ $-42 \pm 3\%$ ($P < 0.001$); average inspiratory flow, $\Delta\dot{V}_1/\Delta\text{PET}_{\text{CO}_2}$ $-25 \pm 8\%$ ($P > 0.05$) and \dot{V}_1 at $\text{PET}_{\text{CO}_2}55$ $-37 \pm 4\%$ ($P < 0.001$) (fig. 2); tidal volume, $\Delta V_T/\Delta\text{PET}_{\text{CO}_2}$ $-26 \pm 11\%$ ($P > 0.05$) and V_T at $\text{PET}_{\text{CO}_2}55$ $-29 \pm 3\%$ ($P < 0.01$); and frequency response, $\Delta f/\Delta\text{PET}_{\text{CO}_2}$ $-56 \pm 46\%$ ($P > 0.05$) and f at $\text{PET}_{\text{CO}_2}55$ $-15 \pm 5\%$ ($P < 0.05$) (fig. 3). A consistent pattern in changes in T_T and its components, T_I and T_E , were absent and, therefore, the changes were not

FIG. 2. Maximal depression of the minute ventilation, slope ($\Delta\dot{V}_I/\text{PET}_{\text{CO}_2}$) and position (\dot{V}_I at PET_{CO_2} of 55) and the average inspiratory flow, slope ($\Delta\bar{V}_I/\text{PET}_{\text{CO}_2}$) and position (\bar{V}_I at PET_{CO_2} of 55) responses to CO_2 at one or two hours following lumbar epidural morphine (0.1 mg/kg) in seven chronic pain patients.



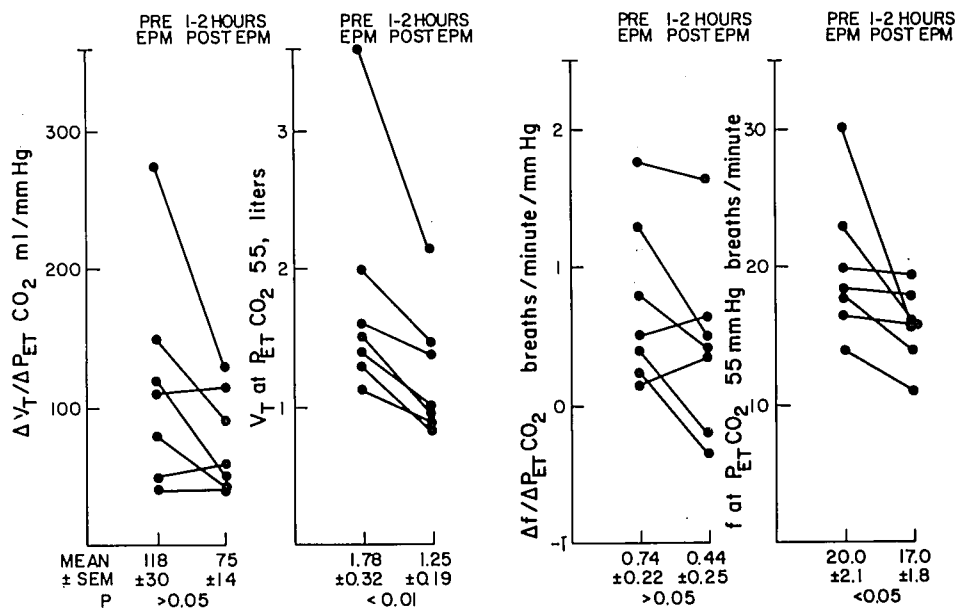
statistically significant. The correlation coefficients between the control slopes of the minute ventilation ($\dot{V}_I/\text{PET}_{\text{CO}_2}$) or the average inspiratory flow ($\bar{V}_I/\text{PET}_{\text{CO}_2}$) and the maximal decrease in these variables, at one or two hours were positive and statistically significant, $r = 0.82$ and 0.93 ($n = 7$), respectively. The correlation coefficients between the plasma morphine concentrations and the per cent decrease in the slopes or the displacement of the minute ventilation, tidal volume, or the average inspiratory flow responses at one or two hours were not significant.

At eight hours postinjection the \dot{V}_I at PET_{CO_2} 55 ($-52 \pm 19\%$ < 0.05), and the \bar{V}_I at PET_{CO_2} 55 ($-36 \pm$

13% , $P < 0.05$) were significantly less than the control values (table 1 and figs. 4 and 5). The displacement of the tidal volume response to CO_2 which was $-27 \pm 18\%$ was not statistically significant ($P > 0.05$). The slopes of the minute ventilation, tidal volume, and the average inspiratory flow responses to CO_2 were not significantly different from the control values. Therefore, epidural morphine results in a reduction in the slope of the minute ventilation response to CO_2 at one and two hours, and at eight hours postinjection the minute ventilation was displaced to the right without a significant reduction in slope (figs. 4 and 5).

At 4, 12, and 24 h neither the slopes nor the positions

FIG. 3. Maximal depression of the tidal volume, slope ($\Delta V_T/\text{PET}_{\text{CO}_2}$) and position (V_T at PET_{CO_2} of 55) and the frequency response, slope ($\Delta f/\text{PET}_{\text{CO}_2}$) and position (f at PET_{CO_2} 55) responses to CO_2 at one or two hours following lumbar epidural morphine (0.1 mg/kg) in seven chronic pain patients.



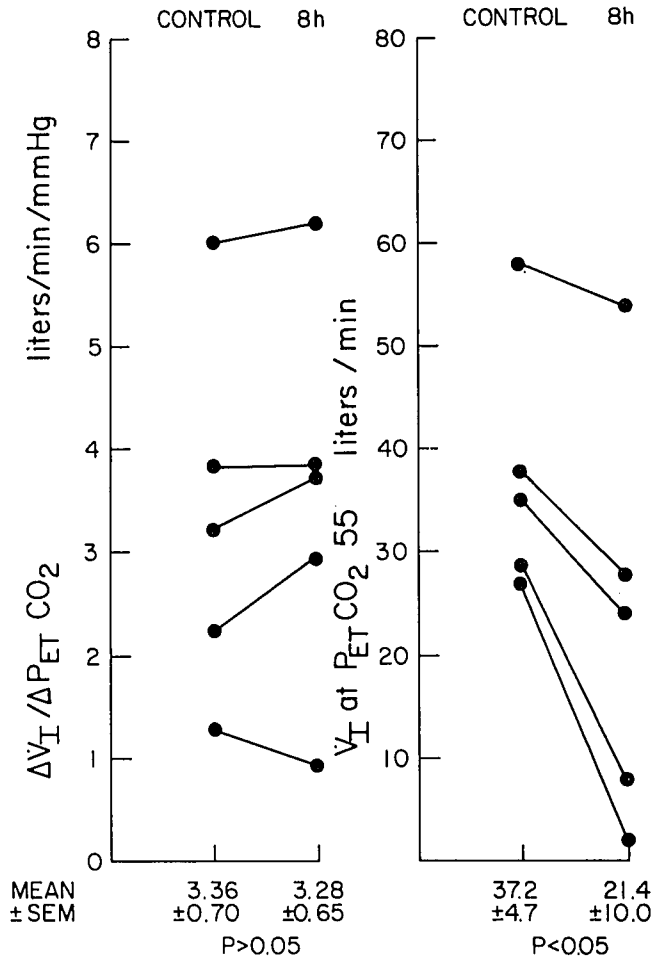


FIG. 4. The slope and displacement of the minute ventilation response to CO₂ at eight hours following lumbar epidural morphine (0.1 mg/kg) in five patients with chronic pain. Two patients were not studied at eight hours (one had received naloxone for respiratory depression and the other was nauseated).

of the minute ventilation and its component responses to CO₂ were significantly different from control values (table 1).

By comparing in individual patients the control and postinjection values for the minute ventilation and its component responses to CO₂ different patterns of response to epidural morphine were evident. All patients demonstrated a reduction in the slope of the minute ventilation responses to CO₂ at one and/or two hours, and in all except one patient the reduction was statistically significant (F test, *P* value range < 0.001–<0.05) (fig. 2). Although there was more variation in the effect of epidural morphine on the slopes of the tidal volume and the average inspiratory flow responses to CO₂, in all patients these responses were displaced to the right (F test, *P* value range < 0.001–0.005) (figs. 2 and 3). The interindividual variation in the response to epidural morphine at 1–2 hours was most obvious in the effects on the slope of the frequency response to CO₂: in five of the seven patients there was a significant reduction in the slopes (F test, *P* value range < 0.005–0.025) and in two the slope increased (fig. 3).

In four of the five patients studied at 8 hours the minute ventilation response to CO₂ was significantly displaced (F test value range *P* < 0.001–0.005) without a statistically significant change in slope (*P* > 0.05) (fig. 4). The segmental level of analgesia did not rise above the first lumbar segment in the patient in whom the minute ventilation response curve was not displaced at 8 hours. Similarly, in all except that patient average inspiratory flow response to CO₂ also was displaced to the right (F test, *P* value range < 0.001–0.005). Therefore, in four of the five subjects studied at 8 hours there was evidence of a biphasic depression of ventilatory control and in one other patient the late phase of ventilatory

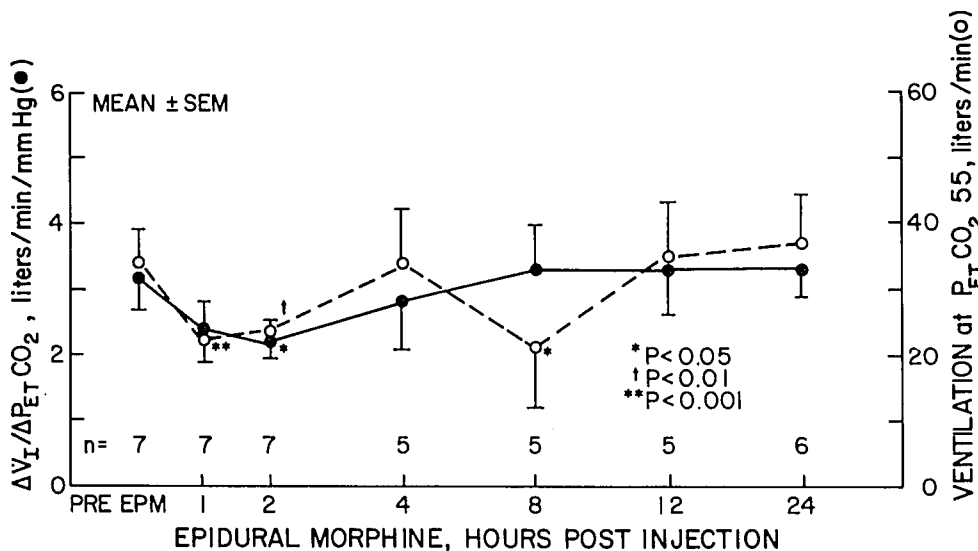


FIG. 5. Biphasic depression of the minute ventilation responses to CO₂ following lumbar epidural morphine (0.1 mg/kg) in seven pain patients. The slope ($\Delta\dot{V}_I/\Delta P_{ETCO_2}$) = closed symbol (●) and the position (\dot{V}_I at $P_{ETCO_2} 55$) = open symbol (○). Values are means \pm SEM. *P* values are for statistical significance of difference from control data. At four and eight hours one patient had severe respiratory depression and at 4, 8, and/or 12 h three patients were nauseated and unable to participate in the rebreathing response to CO₂.

depression was accelerated by coughing. Because that patient had received naloxone the subsequent data were not reported.

Discussion

EFFECTS OF EPIDURAL MORPHINE IN THE VENTILATORY RESPONSES TO CO₂

One to two hours following the administration of epidural morphine the slope of the minute ventilation was reduced and the component responses to CO₂ were displaced to the right. The magnitude of the reduction of the slope of the minute ventilation was similar to that produced by similar doses of morphine administered intramuscularly or subcutaneously.¹⁷⁻¹⁹ The variation between individuals in the reduction of the frequency response to CO₂ is also similar to the effect of intramuscular morphine.¹⁸ We propose that this early phase of depression of control of ventilation is the result of diffusion of morphine into the blood via the epidural veins and circulatory redistribution to the central respiratory control system. During these non-steady state conditions the relationship between plasma and brain morphine concentration is not predictable and, therefore, the correlation coefficient between the peak unconjugated plasma morphine concentrations and the per cent reduction in the slope of the minute ventilation responses to CO₂ was not statistically significant. Rigg and associates also have demonstrated that there is no relationship between the plasma morphine concentration and the reduction in the minute ventilation response to CO₂.²⁰ The rapid onset of pain relief and elevation of mood at one to two hours are also consistent with a circulatory redistribution to the brain. The time course of mood elevation was similar to that described following intramuscular heroin or morphine sulfate.⁸

Our study also has demonstrated a usually late displacement of the minute ventilation response to CO₂ which coincides with the maximal rise in the segmental level of analgesia and loss of skin temperature discrimination. Both the maximal rise in segmental analgesia and the magnitude of late displacement of the minute ventilation response to CO₂ exhibited substantial variation between individuals (fig. 4). In the majority of patients the effect on the minute ventilation response to CO₂ was less marked than the early phase of depression. Therefore, in the absence of any physical perturbation of the CSF the concentration of morphine in the cisterna magna or fourth ventricle which is the result of diffusion along a concentration gradient and possibly also facilitated by transmitted respiratory and cardiovascular motion and reabsorptive process of CSF is low. However, we also observed in a single patient that if the process of upward movement of morphine could be

accelerated, particularly early when the concentration of morphine in the lumbar CSF was high, then a sufficiently high morphine concentration in the CSF bathing the brainstem resulted in severe and prolonged depression of ventilation. Although this depression was reversed by naloxone, it recurred and was again reversed by naloxone. These features of prolonged depression of ventilation by morphine and short duration of reversal by naloxone are consistent with the known pharmacokinetics of morphine and naloxone.²¹

Previous studies on the respiratory effect of epidural morphine^{22,23} or other opiates²⁴ have only examined the early phase of depression of control of ventilation. Following lumbar epidural morphine (10 mg) at one hour postinjection the reduction in the slope of the minute ventilation and the occlusion pressure responses were statistically significant, and at six hours postinjection only the reduction of the slope of the occlusion pressure response was significant.²³ There were no data on the segmental level of analgesia. Bromage and associates noted that after the second dose of thoracic epidural opiates (methadone or hydromorphone) the respiratory depression was greater than after the first dose and was equivalent to the respiratory depression produced by intravenous route of administration.²⁴ Bromage and associates also have reported a rise with time in the segmental level of analgesia following lumbar epidural opiates.²⁵

PLASMA MORPHINE AND PHARMACOKINETICS

Our data show that morphine is absorbed rapidly from the epidural space into the systemic circulation, with a peak plasma morphine (unconjugated) concentration at 15 min postinjection. The plasma morphine concentrations at one hour were similar to those reported by Doblar and associates and Weddel and Ritter, following epidural morphine (10 mg).^{23,26} The latter used a sensitive and specific method of liquid chromatography with electrochemical detection, but their coefficients of variation were large. Our data on the plasma morphine concentrations following epidural morphine, however, do differ from those of Chauvin and associates.²⁷ Following 0.2 mg/kg epidural morphine the rise in plasma morphine concentration was slow, peaked at 1-3 h (>60 ng/ml), and was still greater than 40 ng/ml at 12 h postinjection. We believe that because of the lack of specificity of their radioimmunoassay technique,^{28,29} a substantial amount of morphine glucuronide was measured as morphine. This hypothesis is supported by the similarity of our total plasma morphine curves (morphine plus morphine glucuronide) with their data (fig. 1). The rapid *in vivo* conjugation of morphine with glucuronic acid has been confirmed by sev-

eral previous studies.³⁰⁻³³ The plasma concentrations of unconjugated morphine following epidural morphine were similar to the plasma concentrations following similar doses administered intramuscularly^{30,31} and from 0.25 h postinjection similar to 0.14 mg/kg administered intravenously.³² The morphine plasma half life of 2.38 h determined in this study is also similar to that of unconjugated plasma morphine following intramuscular morphine^{30,31} but longer than the plasma half-life for unconjugated morphine following intravenous administration.^{32,33}

Following lumbar epidural administration of morphine, the concentration of morphine in the lumbar CSF peaks with very high concentrations at two hours (3,550 ng/ml) and falls to 490 ng/ml by 12 h postinjection.³⁴ Morphine, because of its low fat solubility, diffuses slowly into the spinal cord and therefore high concentrations remain in the CSF and diffuse along a concentration gradient cephalad to result in depression of control of ventilation. Other processes which may facilitate the cephalad movement of morphine include transmitted respiratory and cardiovascular motion and the absorptive processes of CSF. Therefore, any perturbation of the CSF which would accelerate cephalad movement such as coughing particularly two to four hours postinjection would result in high concentrations in the cisterna magna. Furthermore, the concentration of morphine administered directly into the cisterna magna which results in depression of the ventilatory response to CO₂ is lower than that administered intravenously.³⁵ In comparison with morphine, fentanyl, a more fat-soluble synthetic opiate, diffuses more rapidly into the spinal cord. The duration of analgesia is short and respiratory depression following epidural fentanyl has not been reported.

PAIN RELIEF, MOOD RESPONSE, AND NON-RESPIRATORY COMPLICATIONS OF EPIDURAL MORPHINE

As has been demonstrated previously, epidural morphine results in prolonged effective pain relief.² The incidences of urinary retention, pruritus, nausea, and vomiting are similar to that reported in other series.^{3,4} Because there was no difficulty with the neuromotor performance of micturition, we conclude that urinary retention results from an absence of awareness of distention of the bladder. The incidence of nausea and vomiting is lower with epidural morphine than the same dose administered intravenously.⁴ However, because of the late onset of nausea in our patients, we considered that it also may have been a manifestation of the cephalad movement of morphine in the CSF to the brainstem. The incidence of pruritus was high, but in the

majority of patients it was not sufficiently severe to interfere with activity or sleep. It is currently thought that epidural morphine causes pruritus as a result of action within the central nervous system possibly because it alters the pattern of sensory signals.^{36,37}

OPIATE ANALGESIA AND RESPIRATORY FUNCTION

Pain relief has always been bought at a price. Parenteral narcotic analgesics depress ventilation, inhibit sighs, and impair both the chemical regulation of ventilation and the neural reflex increase in respiratory drive in response to mechanical loads. Regional analgesia, such as epidural analgesia using local anesthetics, does not impair central respiratory control system but blocks the autonomic efferent system and may impair respiratory neuromotor function. However, due to the complexity of administration and the requirements of monitoring, epidural local analgesia has not been utilized extensively in the management of severe pain such as postoperative pain. Therefore, the demonstration of opiate receptors in the dorsal horn pain pathways,³⁸ analgesia in experimental animals following subarachnoid morphine,³⁹ and that subarachnoid or epidural morphine in humans resulted in prolonged selective analgesia with apparent freedom from serious side effects foreshadowed a major advance in pain management.^{1,2} The administration of opiates into the subarachnoid or epidural space is an innovative and potentially very important approach to the management of severe pain. However, optimal application, mode of administration, and opiates of choice are yet to be determined. Our study has demonstrated that lumbar epidural morphine may result in a biphasic depression of the minute ventilation response to CO₂. We postulate that the early phase of respiratory depression is the result of absorption of morphine into the epidural veins and circulatory redistribution to the brain while a usually occurring late phase is the result of cephalad movement of morphine in the CSF to the brainstem. The latter may be predicted from the rise in the segmental level of analgesia and loss of cutaneous temperature discrimination. An acceleration of this phase results in severe and possibly prolonged depression of control of ventilation because of the relatively high concentration of morphine in the CSF,³⁴ the absence of a blood-brain barrier to diffusion from CSF into the bulbar and pontine respiratory nuclei, and the prolonged retention of morphine in brain tissue.²¹

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