Anesthesiology
55:423-428, 1981

Epidural Morphine Following Epidural Local Anesthesia: Effect on Ventilatory and Airway Occlusion Pressure Responses to CO_2

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The authors measured the minute inspired ventilation ($\dot{V}_I$) and airway occlusion pressure (P_{100}) responses to CO_2 during rebreathing in ten patients who were given epidural morphine for analgesia following lower extremity or lower abdominal surgery. All patients were studied and blood samples for morphine analysis were obtained at four different times: preoperatively, postoperatively premorphine, and one and six hours after a single 10-mg epidural dose of preservative-free morphine in 10 ml of saline. All patients reported effective analgesia with a duration ranging from 8-25.5 h. There were no differences between the pre- and postoperative $\dot{V}_I$ *vs.* P_{CO_2} and P_{100} *vs.* P_{CO_2} response slopes, indicating that the epidural local anesthetic alone had no effect on respiratory drive. Administration of 10 mg morphine epidurally caused a significant 22 per cent decrease in the average $\dot{V}_I$ *vs.* P_{CO_2} slope and a 33 per cent decrease in the average P_{100} *vs.* P_{CO_2} slope one hour postmorphine when compared to the postoperative slopes. The average decrease in $\dot{V}_I$ *vs.* P_{CO_2} at 6 h postmorphine was not significant. The average P_{100} *vs.* P_{CO_2} response slope was decreased significantly at 6 h postmorphine by 27 per cent. There was no significant correlation between serum morphine concentration and the ventilatory responses. The authors conclude that morphine administered by the epidural route produces decreased respiratory drive and that there is a high degree of individual variability in the magnitude and time course of this effect. (Key words: Analgesics: morphine. Anesthetic techniques: epidural narcotics. Carbon dioxide: ventilatory response. Ventilation: airway occlusion pressure; carbon dioxide response.)

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Received from the Departments of Anesthesiology, Physiology and Internal Medicine, Uniformed Services University, Bethesda, Maryland 20014, and the Anesthesia and Operative Service, Walter Reed Army Medical Center, Washington, D. C. 20814. Accepted for publication April 16, 1981. Supported by USUHS Grant RO8000. Presented at the 31st fall meeting of the APS, October 12-17, 1980, Toronto, Canada. Awarded first prize for Current Research by New Investigators at the 34th Postgraduate Assembly in Anesthesiology, New York, New York, December 13-17, 1980.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as reflecting the views of the Department of the Army or the Department of Defense.

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CONSIDERABLE INTEREST has developed in the administration of opiates into both the epidural and intrathecal spaces for the relief of chronic and postoperative pain.[1-5] Administration of the appropriate type and dose of epidural opiate can produce analgesia without significant motor, sensory, or sympathetic nervous system blockade, of duration several times longer than that which results from a single equivalent parenteral dose. Despite the administration of epidural or intrathecal opiates to over 1,200 patients without report of serious complications,[1-6] several investigators have reported respiratory depression after intrathecal morphine[7,8] and after epidural meperidine.[9]

Because of the potential for widespread use of epidural morphine analgesia and numerous reports of its efficacy without respiratory compromise, which are in conflict with other scattered reports of respiratory arrest and/or depression observed in association with the epidural and intrathecal use of opiates, we conducted a controlled study of the effects on the ventilatory response to CO_2 of a single 10-mg dose of preservative-free epidural morphine. Since the output of the ventilatory controller is influenced by the interaction of the chemical and the neuromechanical control systems, we have determined both the $\dot{V}_I$ and P_{100} responses to CO_2 in order to gain insight into the nature of the effect of epidural morphine on ventilatory control. The study design eliminated the influences of premedication, and of intraoperative and postoperative medications, and thus permitted the determination of the effect of epidural morphine alone on ventilatory control. Since the ventilatory response to CO_2 during inspiratory resistive loading may provide additional insight into ventilatory control mechanisms, additional studies were performed with inspiratory flow-resistive loading in three of the ten subjects.

Methods

Studies were conducted in ten patients who gave informed consent in accordance with a protocol approved by the Clinical Investigation Committees at Walter Reed Army Medical Center and at the Uniformed Services University of the Health Sciences. All patients were males between 19 and 38 years of age with unremarkable medical and surgical histories except for the planned

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procedure, and had no history of adverse reaction to any of the medications used in the study. The surgical cases included patients undergoing minor lower abdominal or lower extremity procedures. Prior to being asked to participate in this study, all patients were interviewed by an anesthesiologist, were identified as candidates for epidural anesthesia, and agreed to an epidural anesthetic. All patients were pain-free prior to surgery and were taking no medications before the operation. No patient received any premedication since the drugs used are all known to alter ventilatory control. Any patient requiring intravenous or inhalational supplemental agents for comfort or safety intraoperatively or postoperatively was eliminated from the study. Postoperatively, two patients were withdrawn from the study because they did not experience analgesia with as rapid onset as they desired.

Ventilatory sensitivity to CO_2 was determined using the modified Read rebreathing method.[10] Each patient was studied reclining with the head up at 40°, with a snug noseclip in place, breathing through a rubber mouthpiece. Inspiratory air flow rate, volume of inspired air, airway pressure, and end-tidal P_{CO_2} at the mouth were measured continuously with the subject rebreathing from a 13-l reservoir bag filled with 7 per cent CO_2 in oxygen. Air flow was measured using a Fleisch pneumotachograph (Hewlett-Packard® 21072B), from which volume was derived by electrical integration (Hewlett-Packard® 8815A integrator). Calibration was performed using a one-liter syringe and a rotameter. Airway pressure was measured with a large bore needle inserted into the rubber mouthpiece which was connected to a manometrically calibrated Hewlett-Packard® No. 270 gas differential pressure transducer. Per cent CO_2 in the airway was measured continuously by sampling gas via a second needle from the mouthpiece for analysis with a CO_2 analyzer (Beckman® LB-2) which was calibrated with two analyzed CO_2 mixtures. The sampled gas was returned to the 13-l reservoir bag to maintain constant volume in the rebreathing circuit. In addition to the $\dot{V}_I$ *vs.* P_{CO_2} response curves which were generated, the airway pressure 100 ms after the initiation of a breath against an occluded airway (P_{100})[11-13] was determined as a function of P_{CO_2} by creating silent, intermittent, total occlusions of the airway using a Starling resistor. P_{100}, which is directly related to integrated phrenic nerve output, increases linearly with P_{CO_2} as does $\dot{V}_I$.[11-13] Unlike the $\dot{V}_I$ measurement, however, P_{100} is independent of airway mechanics and respiratory timing because air flow does not occur during the measurement.[11-13] During all studies the EKG was monitored continuously to detect the occurrence of any arrythmia.

Each patient, after breathing room air via the circuit without the reservoir bag attached, was switched to the CO_2 mixture to begin the study. After 2–3 min of equilibration, data were collected until an end-tidal CO_2 of 10 per cent was reached or the patient desired to discontinue the study. As CO_2 concentration increased during rebreathing, intermittent total airway occlusions of 0.5-s duration were done for the P_{100} determination at 20- to 40-s intervals. The identical protocol was followed during each of the four rebreathing studies.

In three of the ten subjects, inspiratory flow-resistive loaded breathing studies were also done at each of the four study periods. For each study period, two CO_2 rebreathing responses were conducted in random order, one without a load resistor and one with a resistance of 25 cm $H_2O \cdot l^{-1} \cdot s^{-1}$ in the inspiratory side of the breathing circuit.

The epidural catheter was inserted at the L4–L5 level and the epidural anesthetic (in nine patients, 500–800 mg chloroprocaine; in one patient, 400 mg chloroprocaine plus 80 mg bupivicaine) was given in the operating room by an anesthesiologist. Postoperatively the patient was taken to the recovery room. To determine if the epidural anesthetic and/or operative procedure affected ventilatory response, the patient underwent a second CO_2 rebreathing study when the local epidural anesthetic level reached the tenth thoracic dermatomal level. Following this study, a single 10-mg dose of preservative-free morphine** diluted in 10 ml of *p*H-adjusted normal saline, was injected into the epidural space. The injection of epidural morphine, which occurred after the second CO_2 response, was administered when the patients complained of discomfort related to the surgical site. No patient complained of more than mild to moderate pain before the dose of epidural morphine was administered. The third CO_2 response study was performed one hour after the epidural morphine injection. The patients were observed in the recovery room until the fourth and final CO_2 rebreathing study was completed six hours after the morphine injection. Immediately after each of the four rebreathing studies in each patient a peripheral venous blood sample was obtained for the determination of serum morphine level. The serum was frozen at −80°C until analyzed by the high-pressure liquid chromatographic method of Wallace *et al.*[14] The sensitivity of this assay is 2 ng/ml.

All ventilatory and EKG data were collected on a Hewlett Packard® eight-channel strip chart recorder screened from the patient's view. Alveolar P_{CO_2}, as estimated from measurements of the end-tidal P_{CO_2}, was averaged over the breaths used in the ventilation calculation for the time interval. Approximately 15 to 20 measurements of ventilation and associated parameters were obtained throughout the study, each being the average of three or four breaths.

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Data were reduced by computing, using least-squares linear regression, the slopes of the lines relating inspiratory minute ventilation and airway occlusion pressure to end-tidal P_{CO_2}. All $\dot{V}_I$ and P_{100} *vs.* P_{CO_2} relationships were linear with correlation coefficients in the range of 0.88 to 0.98 by least-squares linear regression. The assessment of respiratory depression was made by comparison of the one and six hour postmorphine response slopes with the postoperative premorphine response slope. The latter will hereinafter be referred to as the control determination because unlike the preoperative study, it bears a constant temporal relationship to the one and six hour postmorphine studies. Data are presented as mean values ± 1 SEM. For statistical evaluation of the data Student's paired *t* test was applied, and *P* values < 0.05 were considered significant.

Results

After the patients were given epidural morphine they were asked to notify the investigator when the pain that caused them to request analgesia had subsided. They were also asked to indicate when pain at the surgical site recurred. As determined in this manner, onset of analgesia after epidural morphine occurred within 10–45 min and the duration of analgesia ranged from 8–25.5 h.

Tables 1 and 2 give the slopes and intercepts of the $\dot{V}_I$ *vs.* P_{CO_2} and P_{100} *vs.* P_{CO_2} lines obtained for the ten patients. The preoperative $\dot{V}_I$ *vs.* P_{CO_2} response slopes averaged 2.09 ± 0.33 $l \cdot min^{-1} \cdot torr^{-1}$. Postoperatively, but before the administration of epidural morphine, the control $\dot{V}_I$ *vs.* P_{CO_2} slope averaged 1.83 ± 0.22 $l \cdot min^{-1} \cdot torr^{-1}$. The average $\dot{V}_I$ *vs.* P_{CO_2} slope at one hour after morphine (1.46 ± 0.22 $l \cdot min^{-1} \cdot torr^{-1}$) was significantly decreased to 80 per cent of the control value, but the value at six hours after morphine (1.5 ± 0.33 $l \cdot min^{-1} \cdot torr^{-1}$) was not significantly different from the control.

TABLE 1. Inspiratory Minute Ventilation ($\dot{V}_I$) *vs.* End-tidal P_{CO_2}

	Response slopes, $\Delta\dot{V}_I/\Delta P_{CO_2}$ ($l \cdot min^{-1} \cdot torr^{-1}$)			
Patient Number	Preoperative	Postoperative (control)	One Hour Postmorphine	Six Hours Postmorphine
1	2.88	3.01	2.34	2.80
2	1.20	1.72	1.71	1.38
3	3.11	2.16	1.38	0.99
4	1.76	2.18	2.03	3.79
5	1.99	2.00	1.30	1.00
6	2.66	2.11	1.33	0.97
7	4.00	1.86	2.32	1.62
8	1.72	1.71	1.34	1.54
9	0.95	1.10	0.71	0.57
10	0.66	0.45	0.12	0.40
MEAN Slope ± SEM	2.09 ± 0.33	1.83 ± 0.22	1.46* ± 0.22	1.51 ± 0.33
MEAN Intercept ± SEM	40.0 ± 1.5	37.7 ± 1.1	39.8 ± 2.3	39.4 ± 3.0

* Significantly different from the postoperative (control) group, $P < 0.05$.

TABLE 2. Airway Occlusion Pressure (P_{100}) *vs.* End-tidal P_{CO_2}

	Response Slopes, $\Delta P_{100}/\Delta P_{CO_2}$ (cm H_2O/torr)			
Patient Number	Preoperative	Postoperative (control)	One Hour Postmorphine	Six Hours Postmorphine
1	0.51	0.55	0.34	0.32
2	0.41	0.50	0.35	0.48
3	0.73	0.72	0.27	0.33
4	0.56	0.54	0.63	0.81
5	0.60	0.46	0.31	0.09
6	0.44	0.51	0.41	0.42
7	0.82	0.73	0.38	0.51
8	0.20	0.42	0.25	0.26
9	0.44	0.52	0.29	0.28
10	0.15	0.19	0.16	0.16
MEAN Slope ± SEM	0.49 ± 0.07	0.51 ± 0.05	0.34* ± 0.04	0.37* ± 0.06
MEAN Intercept ± SEM	41.9 ± 2.3	41.2 ± 0.97	40.4 ± 1.6	43.6 ± 2.1

* Significantly different from the postoperative (control) group, $P < 0.05$.

The preoperative P_{100} *vs.* P_{CO_2} response slope averaged 0.49 ± 0.07 cm $H_2O \cdot torr^{-1}$, and the postoperative (control) slope averaged 0.51 ± 0.05 cm $H_2O \cdot torr^{-1}$. The average slope one hour postmorphine (0.34 ± 0.04 cm $H_2O \cdot torr^{-1}$) was significantly decreased to 67 per cent of the control slope. At six hours postmorphine the average slope of 0.37 ± 0.06 cm $H_2O \cdot torr^{-1}$ was significantly decreased to 73 per cent of the control slope. There was no significant difference in either $\dot{V}_I$ *vs.* P_{CO_2} or Pa_{CO_2} *vs.* P_{100} intercepts between any of the study periods (tables 1 and 2).

Figure 1 compares the P_{100} *vs.* P_{CO_2} response slopes obtained in three of the ten patients with and without inspiratory flow-resistive loading. Slopes were reduced less below the respective control values in the loaded case than in the nonloaded case.

Serum samples for determination of morphine concentration were obtained from each patient after each study period. The samples obtained prior to injection of morphine revealed no morphine in the serum of any patient. At one hour postinjection, morphine was present in the sera from all patients, with an average serum morphine concentration of 20.2 ± 1.1 ng/ml. Six hours postinjection only five patients had detectable serum morphine levels, which ranged from 4.1–33.2 ng/ml. As illustrated by figures 2 and 3, there was no significant correlation between serum morphine levels and the per-

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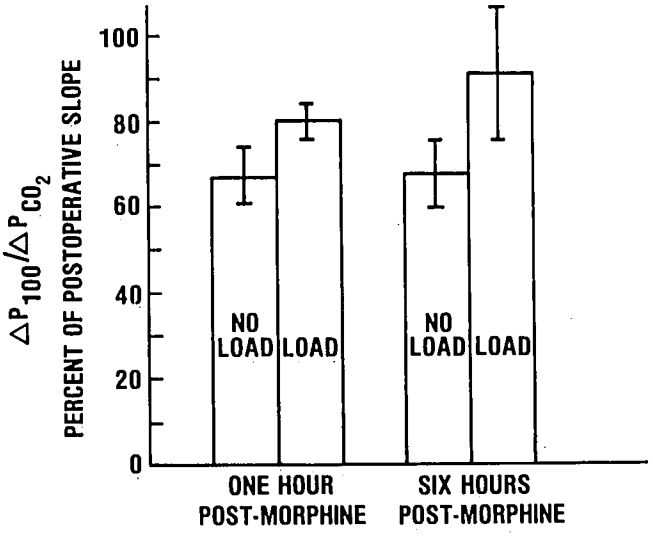

FIG. 1. $\Delta P_{100}/\Delta P_{CO_2}$ response slopes averaged for three patients at one and six hours postmorphine in the nonloaded and inspiratory resistive loaded state expressed as per cent of postoperative premorphine (control) slopes.

centage decrease in the $\dot{V}_I$ *vs.* P_{CO_2} ($R^2 = 0.07$), or P_{100} *vs.* P_{CO_2} ($R^2 = 0.03$) slopes.

Discussion

In this study we determined the effect of a single 10-mg epidural dose of preservative-free morphine in 10 ml

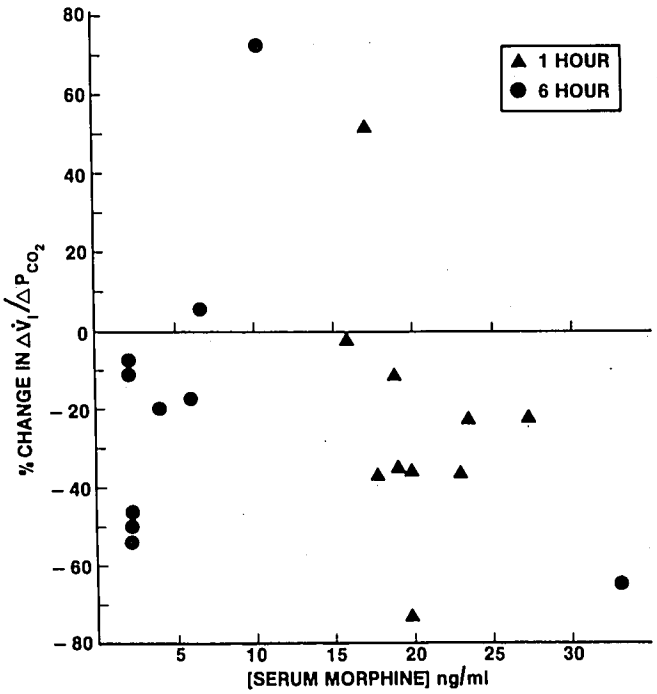

FIG. 2. Change from premorphine control value of $\Delta\dot{V}_I/\Delta P_{CO_2}$ as a function of serum morphine concentration at 1 and 6 h after administration of 10 mg epidural morphine.

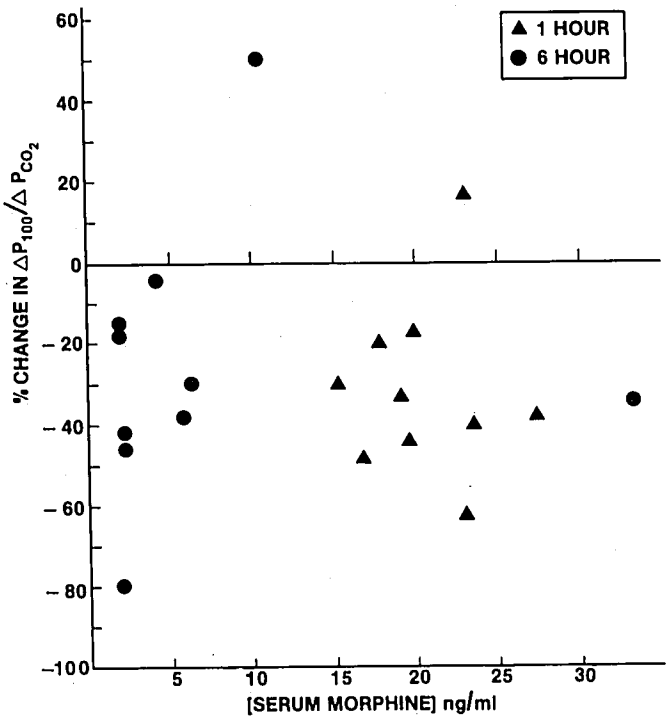

FIG. 3. Change from premorphine control value of ΔP_{100} *vs.* ΔP_{CO_2} as a function of serum morphine concentration at 1 and 6 h after administration of 10 mg epidural morphine.

of *p*H-adjusted saline on the ventilatory and airway occlusion pressure responses to CO_2 by the CO_2 rebreathing technique. The study was designed to avoid the influence of premedication, intraoperative inhalational or intravenous agents, and postoperative analgesic or antiemetic medication on the ventilatory response to CO_2. The surgical site was restricted such that there would be no direct influence on respiratory mechanics and only patients with unremarkable medical and surgical histories were studied. Pain in these patients was not a complicating factor in the interpretation of the data since all patients were pain-free prior to surgery and postoperatively at the time of the CO_2 rebreathing studies, either as a result of the level of epidural local anesthetic during the control study or from the epidural morphine at the one and six hour postmorphine studies. Comparison of the preoperative and the postoperative, premorphine data revealed no significant effect of epidural anesthesia at T10 or lower dermatomal local anesthetic level or of the surgical intervention on the $\dot{V}_I$ or P_{100} *vs.* P_{CO_2} response slopes.

One hour after morphine administration, there were significant decreases in the slopes of the $\dot{V}_I$ and P_{100} responses to CO_2. The observed average 20 per cent reduction in the $\dot{V}_I$ *vs.* P_{CO_2} response slopes one hour after morphine represents a smaller reduction in response than

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the approximately 40 to 50 per cent reduction observed one to three hours after a comparable or smaller parenteral dose in the studies of Weil *et al*,[15] Santiago *et al*,[16] and Torda *et al*.[17] These results suggest that for equivalent dosages at this time interval, epidural morphine produces, on the average, less depression of the $\dot{V}_I$ *vs.* P_{CO_2} response than does parenteral morphine. However, there was considerable individual variation in the ventilatory response to CO_2 in the three studies of parenteral narcotics[15-17] and in the present study as evidenced by a wide range in the per cent reduction in $\dot{V}_I$ *vs.* P_{CO_2} response slopes when examined on an individual basis.

Six hours postmorphine the average $\dot{V}_I$ *vs.* P_{CO_2} response slope was not significantly different from the control slope (table 2), even though eight of the ten subjects demonstrated diminished ventilatory sensitivity to CO_2. The decrease in sensitivity among different patients was highly variable, with some of the patients showing even more respiratory depression at six hours than at one hour. Generalized clinical application of this degree of diminished sensitivity to CO_2 is difficult to define because the response to epidural morphine, like parenteral morphine, demonstrates considerable individual variability. The relationship between resting room air arterial blood-gas tensions (Pa_{O_2} and Pa_{CO_2}) and $\dot{V}_I$ *vs.* P_{CO_2} response slopes has been examined by Santiago *et al*.[16] revealing small but significant increases in Pa_{CO_2} and decreases in Pa_{O_2}. Even this additional correlation must be interpreted in light of the specific clinical situation and cannot be safely extrapolated to a patient with cardiopulmonary disease involving altered ventilatory control. The important implication of our findings, therefore, is that epidural morphine in the present study was found to diminsh ventilatory and airway occlusion pressure sensitivity to CO_2 and that other factors which might predispose any patient to severe respiratory depression should be avoided. It is interesting to note that only combinations of epidural and parenteral narcotics have been documented to produce severe respiratory depression.[8] Thus, it may be necessary to monitor patients for respiratory depression for at least six hours, and possibly as long as the duration of the analgesia.

Our conclusions concerning ventilatory depression are in contrast with those of Torda *et al*.,[17] who in volunteer subjects given epidural morphine, found no statistically significant depression in the $\dot{V}_I$ *vs.* P_{CO_2} response slopes at 1.25 or 3 h postmorphine. Although the lack of significant depression may be related to the smaller dose, 3–4 mg, in contrast to 10 mg, similar per cent changes in the $\dot{V}_I$ *vs.* P_{CO_2} slopes were observed in some of their subjects (three of five subjects were decreased from 24 to 50 per cent at 1.25 and 3 h when compared to control) suggesting that the small number of patients in their study strongly influenced the statistical analysis and therefore their conclusions.

There was no significant correlation between serum morphine concentrations and the degree of respiratory depression, particularly in those patients who demonstrated marked reduction at six hours postmorphine with low serum morphine levels of less than 2 ng/ml. The morphine concentration that would most directly affect ventilation would be that in the brain or cerebrospinal fluid rather than in serum. Thus, the discrepancy between serum morphine concentrations and ventilatory responses in our patients may be due to the fact that serum and brain morphine concentrations did not follow the same time course. Nishitateno *et al*.[18] compared simultaneously measured brain and serum morphine concentrations in dogs. Sixty minutes after intravenous injection of 2 mg/kg morphine, serum levels decreased progressively, while brain morphine levels were relatively constant for up to four hours after injection.

While there was no significant change in either $\dot{V}_I$ *vs.* P_{CO_2} or P_{100} *vs.* P_{CO_2} intercepts, their average values are presented to allow the calculation of $\dot{V}_I$ or P_{100} at any given P_{CO_2} and for the comparison of our data with those of others. The lack of change in the CO_2 intercepts in our study implies that only the sensitivity of the respiratory control system (gain or slope of the response) was altered by epidurally administered morphine without effect on the set point (CO_2 intercept).

Although the studies with resistive loading were conducted in only three of the ten subjects and thus must be considered preliminary in nature, they may provide important insight into the ventilatory depression observed with epidural morphine. In conscious humans, inspiratory flow-resistive loading produces an increase in the P_{100} *vs.* P_{CO_2} response slope when compared to the nonloaded slope,[11-13] presumably due to additional input from peripheral mechanoreceptors. Our data show that the response to loading was not abolished by epidural morphine, a finding similar to that during sleep,[19] after parenteral meperidine,[20] and after parenteral morphine.[16] The relative independence of the $\dot{V}_I$ and the P_{100} responses found with epidural morphine is consistent with our earlier findings.[21]

These data are of potential significance in the application of epidural morphine therapy in postoperative analgesia and treatment of chronic pain. We have demonstrated significant reduction of $\dot{V}_I$ *vs.* P_{CO_2} and P_{100} *vs.* CO_2 responses in conscious humans who did not have any other pharmacological or pathophysiological causes for respiratory depression. In patients who do have decreased respiratory drive or diminished ventilatory reserve for other reasons, such as premedication or intraoperative intravenous supplementation of a regional anesthetic, the physician must be aware that the additive

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effect of epidural morphine analgesia might result in severe respiratory depression.

The authors thank Mr. Steve Van Albert for his assistance with the data reduction and programming and the A. H. Robins Company, Richmond, VA, for their assistance with this study which is part of an FDA-supervised, multicentered group of studies.

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