

## EFFECTS OF INTRATHECAL MORPHINE ON THE VENTILATORY RESPONSE TO HYPOXIA

PETER L. BAILEY, M.D., JEFFREY K. LU, M.D., NATHAN L. PACE, M.D., M.STAT., JOSEPH A. ORR, PH.D., JULIA L. WHITE, R.N., ELIZABETH A. HAMBER, M.D., MATTHEW H. SLAWSON, PH.D., DENNIS J. CROUCH, M.B.A., AND DOUGLAS E. ROLLINS, PH.D.

### ABSTRACT

**Background** Intrathecal administration of morphine produces intense analgesia, but it depresses respiration, an effect that can be life-threatening. Whether intrathecal morphine affects the ventilatory response to hypoxia, however, is not known.

**Methods** We randomly assigned 30 men to receive one of three study treatments in a double-blind fashion: intravenous morphine (0.14 mg per kilogram of body weight) with intrathecal placebo; intrathecal morphine (0.3 mg) with intravenous placebo; or intravenous and intrathecal placebo. The selected doses of intravenous and intrathecal morphine produce similar degrees of analgesia. The ventilatory response to hypercapnia, the subsequent response to acute hypoxia during hypercapnic breathing (targeted end-tidal partial pressures of expired oxygen and carbon dioxide, 45 mm Hg), and the plasma levels of morphine and morphine metabolites were measured at base line (before drug administration) and 1, 2, 4, 6, 8, 10, and 12 hours after drug administration.

**Results** At base line, the mean ( $\pm$ SD) values for the ventilatory response to hypoxia (calculated as the difference between the minute ventilation during the second full minute of hypoxia and the fifth minute of hypercapnic ventilation) were similar in the three groups:  $38.3 \pm 23.2$  liters per minute in the placebo group,  $33.5 \pm 16.4$  liters per minute in the intravenous-morphine group, and  $30.2 \pm 11.6$  liters per minute in the intrathecal-morphine group ( $P=0.61$ ). The overall ventilatory response to hypoxia (the area under the curve) was significantly lower after either intravenous morphine ( $20.2 \pm 10.8$  liters per minute) or intrathecal morphine ( $14.5 \pm 6.4$  liters per minute) than after placebo ( $36.8 \pm 19.2$  liters per minute) ( $P=0.003$ ). Twelve hours after treatment, the ventilatory response to hypoxia in the intrathecal-morphine group ( $19.9 \pm 8.9$  liters per minute), but not in the intravenous-morphine group ( $30.5 \pm 15.8$  liters per minute), remained significantly depressed as compared with the response in the placebo group ( $40.9 \pm 19.0$  liters per minute) ( $P=0.02$  for intrathecal morphine vs. placebo). Plasma concentrations of morphine and morphine metabolites either were not detectable after intrathecal morphine or were much lower after intrathecal morphine than after intravenous morphine.

**Conclusions** Depression of the ventilatory response to hypoxia after the administration of intrathecal morphine is similar in magnitude to, but longer-lasting than, that after the administration of an equianalgesic dose of intravenous morphine. (N Engl J Med 2000; 343:1228-34.)

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OPIOIDS are important analgesic drugs,<sup>1,2</sup> but they depress respiration and in particular the ventilatory response to hypoxia. Whether the effects of opioids on the ventilatory response to hypoxia are mediated peripherally or centrally is not known.<sup>3</sup> Although the ventilatory response to hypoxia is initiated in the periphery, primarily in the carotid bodies, it is possible that centrally mediated opioid actions affect this response. Morphine is by far the most commonly administered intrathecal opioid, so its actions are of particular interest. In addition, because morphine is hydrophilic and is largely retained in the cerebrospinal fluid after intrathecal administration, a comparison of intrathecal and intravenous administration of this drug is a suitable approach to questions about the central and peripheral actions of opioids. In this study, we assessed the effects of intrathecal morphine on the ventilatory response to acute hypoxia in normal men.

### METHODS

#### Study Protocol

From February 1997 through March 1998, we studied 30 normal men ranging in age from 18 to 45 years. Men were excluded if they had a history of tobacco or drug use, alcohol abuse, or low back pain or other back problems; if they had an allergy to opioids; or if their body weight was more than 30 percent above their ideal body weight for age and height. The men were asked not to consume caffeine during the 24 hours before testing began. The study was approved by the institutional review committee of the University of Utah, and all the men gave written informed consent.

The men were randomly assigned to receive one of three treatments: 0.3 mg of preservative-free morphine given intrathecally and placebo given intravenously; placebo given intrathecally and 0.14 mg of morphine per kilogram of body weight given intravenously; or placebo given both intrathecally and intravenously. Each man received only one of these three treatments and therefore was studied only once. The doses of morphine chosen are those commonly used in practice, and they result in similar degrees of analgesia. Neither the men nor the investigators were aware of the treatment assignments.

After base-line tests of ventilatory drive were performed, the men were placed in a lateral position and the low back area was cleaned with povidone-iodine and draped. After local anesthesia had been provided with 1.0 ml of 1 percent lidocaine, subarachnoid puncture was performed with a 25-gauge needle at the L3-4 inter-

From the Department of Anesthesiology, University of Rochester, Rochester, N.Y. (P.L.B.); and the Departments of Anesthesiology (J.K.L., N.L.P., J.A.O., J.L.W., E.A.H.) and Pharmacology and Toxicology (M.H.S., D.J.C., D.E.R.), University of Utah, Salt Lake City. Address reprint requests to Dr. Bailey at the Department of Anesthesiology, University of Rochester, 601 Elmwood Ave., Box 604, Rochester, NY 14642, or at peter\_bailey@urmc.rochester.edu.

space, and the assigned intrathecal treatment was administered. The needle was then removed, and the men resumed a supine position with the back at a 30-degree angle. Intrathecal morphine or placebo was given in a 1-ml volume combined with 1 ml of aspirated cerebrospinal fluid, and injection was performed over a 30-second period. Intravenous morphine or placebo was given in a 5-ml volume, administered over a two-minute period by syringe pump at the same time as the intrathecal injection.

### Tests of Ventilatory Drive

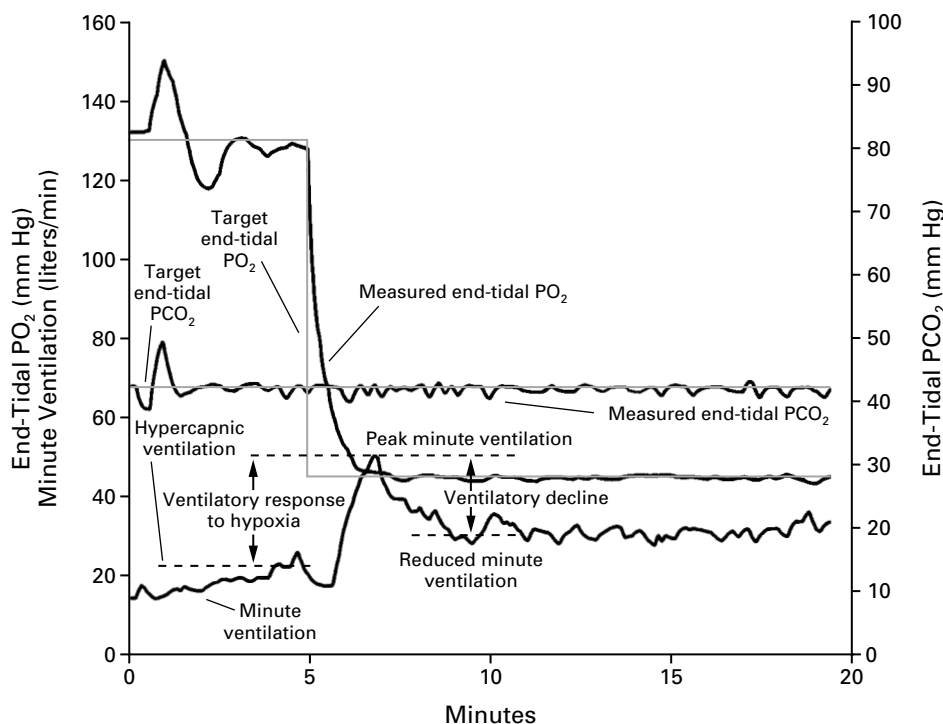
Before the study, the men were familiarized with the procedures they would undergo during testing of the ventilatory response to hypoxia. On the day of study, intravenous and radial-artery catheters were inserted. Before and 1, 2, 4, 6, 8, 10, and 12 hours after study-drug administration, ventilatory tests were performed and arterial blood was sampled for measurement of morphine and its metabolites. The men breathed through a face mask (Vital Signs, Totowa, N.J.). An exercise pneumotachometer capable of measuring flow rates up to 800 liters per minute (Hans Rudolph, Kansas City, Mo.), heated to 38°C and calibrated with a 3-liter syringe (model 5530, Hans Rudolph), and a differential pressure transducer (model CD-15, Validyne, Northridge, Calif.) were used to determine ventilatory flow rates, corrected to body temperature, pressure, and saturated water-vapor pressure. End-tidal expired oxygen and carbon dioxide were measured in samples obtained near the mouth at a rate of 100 ml per minute and tested with paramagnetic oxygen and infrared carbon dioxide analyzers (Datex, Tewksbury, Mass.). Voltages corresponding to the percentages of oxygen and carbon dioxide were digitized and converted to partial pressures with the use of constant values obtained by periodic three-

point calibrations with gas standards. A computer was used to achieve targeted gas partial pressures.

Five minutes before each challenge with hypoxia, the men breathed a hypercapnic mixture of gas with a target end-tidal partial pressure of carbon dioxide of 45 mm Hg and a target end-tidal partial pressure of oxygen of 125 mm Hg. This level of hypercapnia was chosen on the basis of previous studies<sup>4,5</sup> that suggested that the end-tidal partial pressure of carbon dioxide would not increase to more than 45 mm Hg after the administration of the doses of morphine selected in the current study. After 5 minutes of hypercapnic breathing, hypoxia was induced within 1 minute and then maintained for approximately 15 minutes, with a target end-tidal partial pressure of oxygen of 45 mm Hg, which would result in a median oxygen saturation of 78 percent, as measured by pulse oximetry. The target end-tidal partial pressure of carbon dioxide was maintained at 45 mm Hg throughout the challenge with hypoxia. This allowed control of the effects of both hypercapnia and the hypercapnia-hypoxia interaction, effects that could otherwise confound the interpretation of the data on the ventilatory response to hypoxia. The level of hypoxia used in this study has been used in respiratory research for several decades without reported adverse effects. Breath-by-breath, minute ventilation was measured, and the results were stored electronically. Between challenges with hypoxia, the men breathed supplemental oxygen in order to expedite recovery.<sup>6</sup> A typical biphasic ventilatory response to hypoxia as recorded in our laboratory is shown in Figure 1.

### Plasma Levels of Morphine and Morphine Metabolites

The concentrations of morphine and its metabolites (morphine-3-glucuronide and morphine-6-glucuronide) were measured in sam-



**Figure 1.** A Typical Biphasic Ventilatory Response to Hypoxia.

Initially, hypercapnia increases minute ventilation. With the onset of acute hypoxia, a ventilatory response to hypoxia further increases minute ventilation. Within 5 to 10 minutes after the onset of hypoxia, there is ventilatory decline in response to hypoxia.  $PO_2$  and  $PCO_2$  denote the partial pressures of oxygen and carbon dioxide, respectively. The  $PO_2$  and  $PCO_2$  values shown differ slightly from the target values used in the study.

ples of plasma by high-performance liquid chromatography, as described previously.<sup>7</sup> The limits of detection were 500 pg per milliliter for morphine and 250 pg per milliliter for morphine-3-glucuronide and for morphine-6-glucuronide.

Twelve hours after the administration of the study drugs, data collection ceased. The men were monitored until all signs of opioid action had dissipated.

### End Points

To smooth the breath-to-breath variations in minute ventilation, we calculated nonoverlapping, one-minute arithmetic averages of this variable from the start of hypercapnic breathing to the termination of hypoxic breathing. Three distinct one-minute periods were used to characterize ventilatory responses: minute ventilation during the fifth full minute of hypercapnia, which we defined as peak hypercapnic ventilation; minute ventilation during the second full minute of hypoxia, defined as peak ventilation during hypoxia; and minute ventilation during the last full minute of hypoxia, defined as the reduced ventilation associated with the ventilatory decline in response to hypoxia. The ventilatory response to hypoxia was then defined as the difference between the peak ventilation during hypoxia and hypercapnic ventilation. The ventilatory decline in response to hypoxia was calculated as the difference between the peak ventilation and the reduced ventilation.<sup>8</sup> The values for hypercapnic ventilation, the ventilatory response to acute hypoxia, and the hypoxic ventilatory decline were of primary interest.

### Statistical Analysis

Serial measurements of hypercapnic ventilation, the ventilatory response to hypoxia, and the ventilatory decline in response to hypoxia for each of the eight challenges with hypoxia (immediately before drug administration [base line] and 1, 2, 4, 6, 8, 10, and 12 hours thereafter) were used for analysis. For each man, the seven values obtained for each variable after drug administration (i.e., at 1, 2, 4, 6, 8, 10, and 12 hours) were integrated as an area under the curve and standardized as an 11-hour average to characterize the overall effect of the study drug.<sup>9</sup> The lowest values for hypercapnic ventilation and for the ventilatory response to hypoxia after drug administration were determined in order to characterize the greatest drug effect.

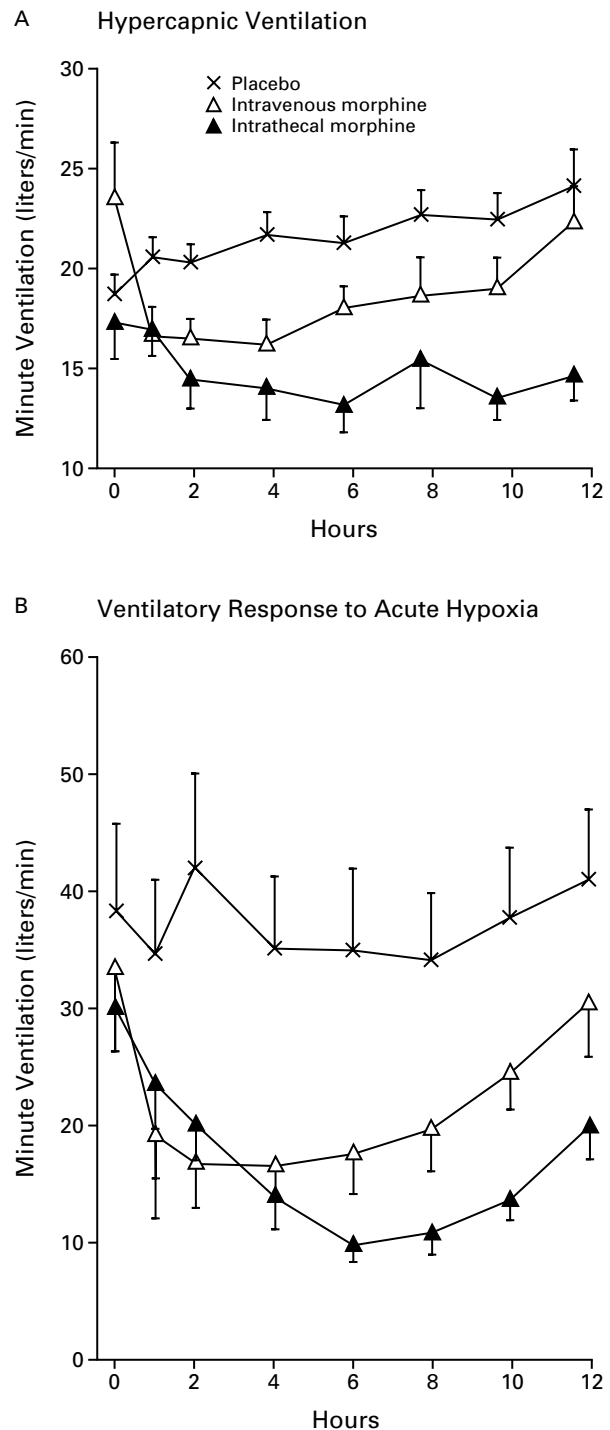
For each variable, an overall comparison of the three treatment groups with respect to the values before drug administration, the values for the overall effect and the greatest effect, and the values at hour 12 was performed by one-way analysis of variance, followed by adjusted pairwise comparisons between groups. The time to the greatest drug effect was also determined. The effects of intravenous morphine and intrathecal morphine were compared by Wilcoxon–Mann–Whitney tests with Hodges–Lehmann estimates of the median differences and interquartile ranges.

The demographic characteristics of the men (age, weight, height, hematocrit, and body-mass index [the weight in kilograms divided by the square of the height in meters]) were compared among the three groups by one-way analysis of variance. Plasma levels of morphine and morphine metabolites were compared between the intravenous-morphine and intrathecal-morphine groups at each sampling time by Wilcoxon's rank-sum test with Bonferroni's adjustment.

Statistical analysis was performed with nQuery Advisor (version 3.0, Statistical Solutions, Cork, Ireland), S-PLUS (version 5.1, MathSoft, Seattle), and StatXact (version 4, Cytel Software, Cambridge, Mass.). All statistical tests were two-sided. Results are expressed as means  $\pm$  SD or as medians and interquartile ranges.

## RESULTS

The mean age of the 30 men was  $26.0 \pm 4.4$  years, their mean weight  $77.3 \pm 10.9$  kg, their mean height  $179.8 \pm 6.1$  cm, their mean body-mass index  $23.9 \pm 3.1$ , and their mean hematocrit  $46.0 \pm 2.6$  percent. There were no differences between the groups in any



**Figure 2.** Time Course of Hypercapnic Ventilation (Panel A) and of the Ventilatory Response to Acute Hypoxia (Panel B) in the Three Treatment Groups. Values are means  $\pm$  SE.

of these variables. Nine men received intrathecal morphine, 11 intravenous morphine, and 10 both intrathecal and intravenous placebo. All the men who received intrathecal morphine had generalized pruritus, whereas pruritus occurred only at the site of injection in the men who received intravenous morphine. Four of the men who received intrathecal morphine had urinary retention, which necessitated bladder catheterization in one of them. In all three groups, other adverse effects were nausea (in eight men) and headache (in four).

The base-line values during hypercapnic ventilation in the treatment groups were similar. After study-drug administration, there was a significant difference in the overall effect of treatment on hypercapnic ventilation only between the intrathecal-morphine group and the placebo group. Hypercapnic ventilation was depressed to a significantly lower minimal value in both the intrathecal-morphine and intravenous-morphine groups than in the placebo group. The maximal depression in hypercapnic ventilation (i.e., the lowest minimal value) was observed significantly earlier after intravenous morphine than after intrathecal morphine (median time to maximal depression, 3 hours [interquartile range, 2 to 4] vs. 6 hours [interquartile range, 5 to 7];  $P=0.02$ ) (Fig. 2). Only in the intrathecal-morphine group was hypercapnic ventilation still significantly depressed at the 12th hour of study as compared with that in the placebo group.

The ventilatory response to acute hypoxia (in terms of the overall effect and the minimal value) was significantly depressed after either intravenous or intrathecal administration of morphine as compared with

placebo (Table 1). The median time to the maximal depression of the ventilatory response to hypoxia in the intravenous-morphine group was 3.5 hours (interquartile range, 2 to 6), as compared with 7 hours (interquartile range, 6 to 8) in the intrathecal-morphine group ( $P=0.06$ ) (Fig. 2). Only in the intrathecal-morphine group was the ventilatory response to hypoxia still significantly depressed as compared with that in the placebo group at the 12th hour of study.

The automatic control of the end-tidal partial pressures of oxygen and carbon dioxide kept the actual values close to the target values in all three study groups. The median end-tidal partial pressure of carbon dioxide in the three groups combined was equal to the target value of 45 mm Hg (interquartile range, 44 to 46) during hypercapnic breathing both at base line and after the induction of hypoxia. The median end-tidal partial pressure of oxygen in the three groups combined was 125 mm Hg (interquartile range, 121 to 128) during hypercapnia at base line and 44 mm Hg (interquartile range, 43 to 46) after the induction of hypoxia.

At base line, the mean ventilatory decline in response to hypoxia was  $4.4 \pm 14.8$  liters per minute, a value that was not significantly different from zero ( $P=0.12$ ). After study-drug administration, the mean ventilatory decline was  $5.1 \pm 8.6$  liters per minute, a value that was significantly different from zero ( $P=0.004$ ). There were no significant differences in the degree of ventilatory decline in response to hypoxia among the three groups at any time. On average, the plasma concentrations of morphine and its metabolites were higher in the intravenous-morphine group

**TABLE 1.** MINUTE VENTILATION BEFORE AND AFTER THE ADMINISTRATION OF INTRAVENOUS MORPHINE, INTRATHECAL MORPHINE, OR PLACEBO IN 30 NORMAL MEN.\*

GROUP	HYPERCAPNIC VENTILATION				VENTILATORY RESPONSE TO HYPOXIA			
	BASE-LINE VALUE	OVERALL EFFECT	MINIMAL VALUE	VALUE AT HR 12	BASE-LINE VALUE	OVERALL EFFECT	MINIMAL VALUE	VALUE AT HR 12
	liters per minute							
Placebo (n=10)	18.7±3.1	22.0±3.4	18.7±2.5	24.3±5.8	38.3±23.2	36.8±19.2	27.1±17.1	40.9±19.0
Intravenous morphine (n=11)	23.6±9.1	18.2±4.2	15.2±3.4†	22.5±5.9	33.5±16.4	20.2±10.8‡	13.7±8.1‡	30.5±15.8
Intrathecal morphine (n=9)	17.4±5.7	14.4±4.4§	11.8±3.5	14.8±4.1¶	30.2±11.6	14.5±6.4‡	8.3±4.1‡	19.9±8.9

\*Plus-minus values are means  $\pm$ SD. Hypercapnic ventilation is the minute ventilation during the fifth minute of hypercapnia, and the ventilatory response to hypoxia is the minute ventilation during the second full minute of hypoxia, minus the hypercapnic ventilation. For each of these two variables, the following values were assessed: the base-line value, which is the result of the ventilatory test performed immediately before the administration of the drugs; the overall effect, which is the time-weighted average (area under the curve) of the values obtained for the seven challenges with hypoxia after drug administration; the minimal value, which is the lowest value after drug administration; and the last value, obtained 12 hours after drug administration. P values were calculated by one-way analysis of variance, and significant differences were estimated by pairwise group comparisons adjusted by Tukey's and simulation-based methods.

† $P<0.001$  for the comparison with placebo.

‡ $P=0.003$  for the comparison with placebo.

§ $P=0.001$  for the comparison with placebo.

¶ $P=0.002$  for the comparison with placebo.

|| $P=0.02$  for the comparison with placebo.

than in the intrathecal-morphine group by at least one order of magnitude at all times (Fig. 3).

### DISCUSSION

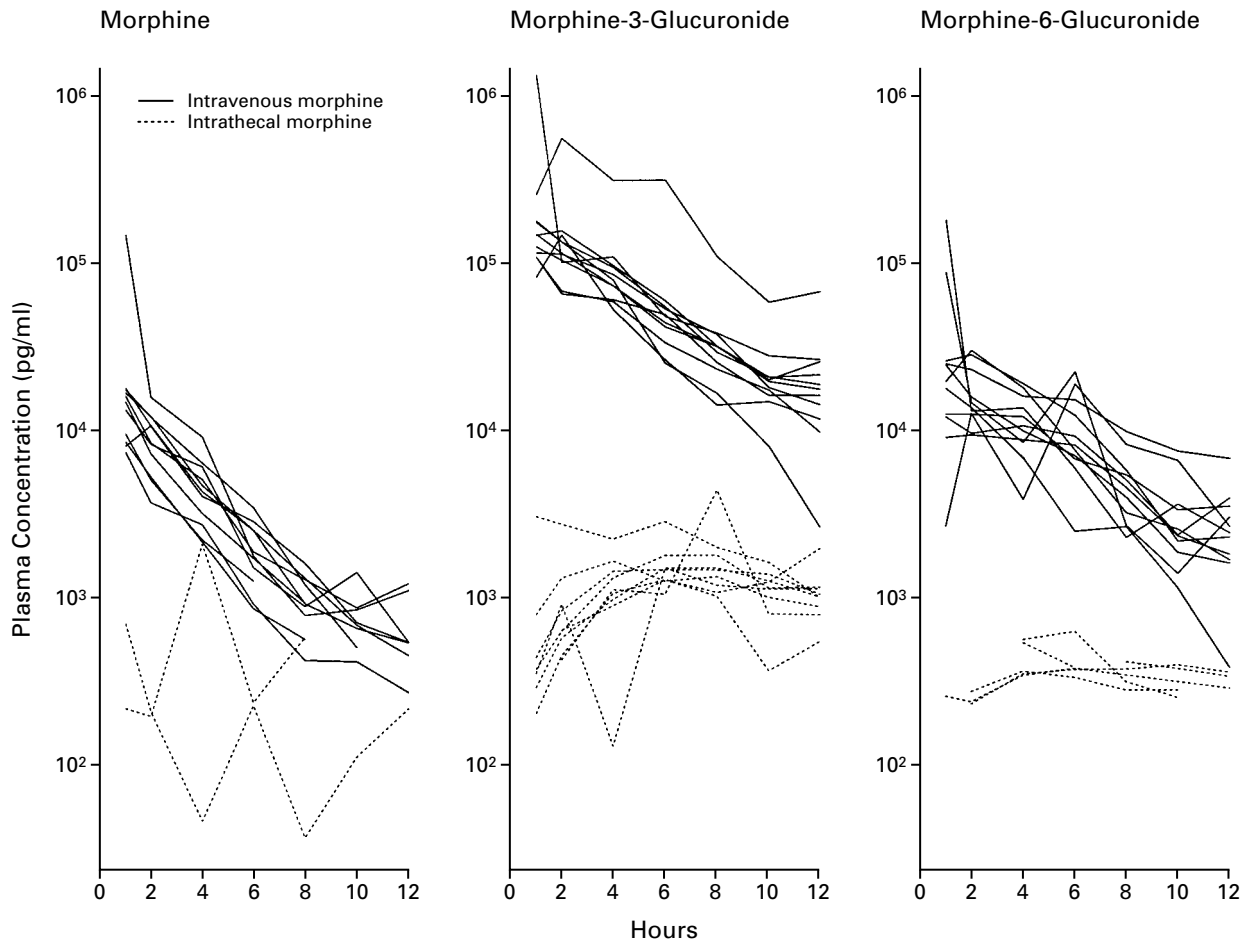
The risks associated with opioid analgesia and its adverse effects continue to be a concern. In particular, opioid-induced respiratory depression after surgery can be severe and life-threatening.<sup>10,11</sup> It is well recognized that the ventilatory response to carbon dioxide is depressed by opioids, but whether depression of the ventilatory response to hypoxia contributes to postoperative respiratory depression is less clear. The uncommon but serious nature of opioid-induced respiratory depression and our incomplete understanding of this phenomenon are reasons why clinicians continue to hesitate to prescribe opioid analgesics.<sup>12,13</sup>

Evidence that opioids have a direct action on the spinal cord<sup>14</sup> led to the intrathecal administration of

opioids to relieve pain.<sup>15</sup> Subsequent reports indicated that the doses of intrathecal morphine initially thought to be appropriate (1.0 to 5.0 mg) were excessive<sup>4,16,17</sup> and that even small doses of intrathecal morphine (0.2 to 0.6 mg) caused substantial, and in some cases profound, respiratory depression.

The ventilatory response to hypoxia is thought to be a vital secondary, or "backup," chemical reflex that protects people from hypoventilation and increasingly severe hypoxia. Although the reflex does not operate at rest under normal conditions, progressive hypoxia elicits a nonlinear increase in ventilation.<sup>18</sup> This increase is known to be inhibited by morphine and other opioids.<sup>19-23</sup>

We found that opioid-induced depression of the ventilatory response to acute hypoxia is mediated exclusively through actions within the central nervous system. Our data do not refute the literature documenting that opioids can influence the ventilatory



**Figure 3.** Time Course of Plasma Concentrations of Morphine and Its Metabolites after Intravenous or Intrathecal Administration of Morphine.

Concentrations are plotted on a logarithmic scale. Of the nine men who received intrathecal morphine, two, nine, and seven had measurable concentrations of morphine, morphine-3-glucuronide, and morphine-6-glucuronide, respectively. All the men who received intravenous morphine had measurable plasma concentrations of morphine and its metabolites throughout the study.

response to hypoxia through peripheral, chemoreceptor-mediated mechanisms.<sup>24</sup> However, our data suggest that systemically administered opioids may lessen the ventilatory response to hypoxia principally by direct actions on the central nervous system rather than on the peripheral nervous system. In addition, the extent to which the ventilatory response to hypoxia was depressed by a commonly used dose of intrathecal morphine was at least as great as that caused by an analgesic dose of intravenous morphine, and the duration of the effect was longer with intrathecal administration.

Morphine is a hydrophilic compound, and therefore intrathecal morphine is almost **completely retained** within the cerebrospinal fluid; the result, as we found, is very low or **undetectable plasma** drug concentrations.<sup>25</sup> Thus, it is conceivable that intrathecal morphine does not alter the peripherally mediated reflex that produces the ventilatory response to hypoxia, a characteristic that could represent an added safety factor in patients treated with intrathecal morphine. However, we found that, because of the centrally mediated actions of intrathecal morphine, the **absence** of a **peripheral** opioid **action** did not **preserve** the reflex in response to hypoxia. Most other opioids used in clinical practice are lipophilic, rather than hydrophilic. Lipophilic opioids are less likely than hydrophilic opioids such as morphine to be retained within the central nervous system after intrathecal injection, and their rostral spread within the central nervous system is much less extensive. On the other hand, after intrathecal injection, lipophilic opioids are more likely to be absorbed into the bloodstream, where they can exert effects on the central nervous system after systemic distribution.

The time course of the effect and, in particular, the time to the peak depression of the ventilatory response to hypoxia were **similar** to those of the ventilatory response to carbon dioxide after intrathecal morphine.<sup>4</sup> This similarity suggests that a **common mechanism** may underlie these responses and that they may have the same central site of action. Our study does not shed light on where in the central nervous system this site might be. We also did not assess the effects of other potentially important factors, such as sleepiness, which can depress breathing in a clinically important manner when superimposed on opioid-induced respiratory depression.

Although a biphasic ventilatory response to hypoxia has been reported in humans,<sup>26-28</sup> we did not consistently detect ventilatory decline in response to hypoxia. There is no clear explanation for this finding. Although the respiratory apparatus used in our study differed somewhat from that used by others,<sup>29,30</sup> we did achieve the target end-tidal partial pressures of oxygen and carbon dioxide within one minute after the apparatus was set to reach these points. In addition, the maintenance of the target partial pressures

and the variability within each test of the response to hypoxia were similar to those with other methods (Ward D: personal communication).

We conclude that opioid-induced depression of the hypoxic ventilatory response in humans is **centrally**, and **not peripherally**, mediated. This action probably contributes to the risk of respiratory depression associated with opioid analgesia.

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