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## Disposition and Respiratory Effects of Intrathecal Morphine in Children

David G. Nichols, M.D.,\* Myron Yaster, M.D.,\* Anne M. Lynn, M.D.,† Mark A. Helfaer, M.D.,‡ Jayant K. Deshpande, M.D.,§ Paul N. Manson, M.D.,¶ Benjamin S. Carson, M.D.,\*\* Michael Bezman, M.D.,†† Lynne G. Maxwell, M.D.,‡ Joseph D. Tobias, M.D.,§ Louise B. Grochow, M.D.‡‡

This article is accompanied by a Highlight. Please see this issue of ANESTHESIOLOGY, page 25A.

\* Associate Professor, Departments of Anesthesiology and Critical Care Medicine and Pediatrics, The Johns Hopkins University School of Medicine.

† Associate Professor, Department of Anesthesiology, Children's Hospital and Medical Center.

‡ Assistant Professor, Department of Anesthesiology and Critical Care Medicine and Pediatrics, The Johns Hopkins University School of Medicine.

§ Associate Professor, Departments of Anesthesiology and Pediatrics, Vanderbilt University School of Medicine.

¶ Professor of Plastic Surgery, The Johns Hopkins University School of Medicine.

\*\* Associate Professor, Departments of Neurological Surgery, Oncology, and Pediatrics, The Johns Hopkins University School of Medicine.

†† Research Associate, Department of Anesthesiology and Critical Care Medicine, The Johns Hopkins University School of Medicine.

‡‡ Associate Professor, Department of Oncology, Division of Pharmacology and Experimental Therapeutics, The Johns Hopkins University School of Medicine.

Received from the Departments of Anesthesiology and Critical Care Medicine, Pediatrics, Plastic Surgery, Neurological Surgery, and Oncology, and the Division of Pharmacology and Experimental Therapeutics, The Johns Hopkins University School of Medicine, Baltimore, Maryland; the Department of Anesthesiology, Children's Hospital and Medical Center, Seattle, Washington; and the Departments of Anesthesiology and Pediatrics, Vanderbilt University School of Medicine, Nashville, Tennessee. Accepted for publication June 21, 1993. Presented in part at the annual meeting of the American Society of Anesthesiologists, Las Vegas, Nevada, October 18-24, 1990.

Address reprint requests to Dr. Nichols: Departments of Anesthesiology and Critical Care Medicine and Pediatrics, The Johns Hopkins University School of Medicine, CMSC 7-100, 600 North Wolfe Street, Baltimore, Maryland 21205.

**Background:** The extent and duration of respiratory depression after opioid administration are poorly defined in infants and children.

**Methods:** The disposition and respiratory effects of intrathecal morphine were studied in ten patients (ages 4 months-15 yr) after repair of craniofacial defects. Morphine, 0.02 mg/kg, was administered intrathecally before the end of surgery. Postoperatively, we determined the minute ventilation ( $V_E$ ) in response to increasing partial pressure of end-tidal carbon dioxide ( $PET_{CO_2}$ ) during carbon dioxide rebreathing. The slope ( $V_E/PET_{CO_2}$ ) and intercept ( $V_E$  at  $PET_{CO_2}$  60 mmHg,  $V_E$  60) of the carbon dioxide response curve were calculated at 6, 12, and 18 h after morphine administration. Cerebrospinal fluid (CSF) and blood were analyzed for morphine concentration by radioimmunoassay.

**Results:** Mean  $V_E/PET_{CO_2}$  decreased from a preoperative value of  $35.1 \pm 3.7$  to  $16.3 \pm 2.8$  ml  $\cdot$  kg $^{-1}$   $\cdot$  min $^{-1}$   $\cdot$  mmHg $^{-1}$  at 6 h after morphine, and remained depressed to  $23.4 \pm 2.9$  and  $23.5 \pm 3.3$  ml  $\cdot$  kg $^{-1}$   $\cdot$  min $^{-1}$   $\cdot$  mmHg $^{-1}$  at 12 h and 18 h, respectively, compared to preoperatively. The infants' ( $n = 3$ )  $V_E/PET_{CO_2}$  at 6 h were 21, 4, and 27 ml  $\cdot$  kg $^{-1}$   $\cdot$  min $^{-1}$   $\cdot$  mmHg $^{-1}$ . Mean  $V_E$  60 decreased from  $874 \pm 125$  to  $276 \pm 32$  ml  $\cdot$  kg $^{-1}$   $\cdot$  min $^{-1}$  at 6 h, but then recovered at 12 and 18 h to  $491 \pm 68$  and  $567 \pm 82$  ml  $\cdot$  kg $^{-1}$   $\cdot$  min $^{-1}$ , respectively. The infants'  $V_E$  60 at 6 h were 350, 142, and 245 ml  $\cdot$  kg $^{-1}$   $\cdot$  min $^{-1}$ . Mean CSF morphine concentration was  $2,860 \pm 540$  ng/ml at 6 h, and decreased to  $640 \pm 220$  and  $220 \pm 150$  ng/ml at 12 and 18 h, respectively.

**Conclusions:** Intrathecal morphine, 0.02 mg/kg, depressed the ventilatory response to carbon dioxide for up to 18 h concomitant with increased CSF morphine concentrations. Infants (4-12 months of age) did not exhibit greater ventilatory depression than did children (2-15 yr of age). (Key words: Analgesia, postoperative. Analgesics, opioid: intrathecal morphine. Anesthesia, pediatric. Cerebrospinal fluid. Pharmacodynamics. Ventilation, carbon dioxide response.)

SEVERAL studies have documented that infants and children experience pain after operations, and that pain is associated with a hormonal stress response similar to that observed in adults.<sup>1,2</sup> Recognition of this fact has made it desirable to find safe ways of administering opioid analgesics in the postoperative state. Epidural and intrathecal morphine have provided long-lasting analgesia to adults and children.<sup>3,4</sup> However, respira-

tory depression after opioid administration remains a well recognized complication.<sup>5</sup> Some studies have indicated that infants are particularly vulnerable to respiratory depression after opioid administration.<sup>6-8</sup> Safe usage of opioids in infants and children would be facilitated by better understanding of the extent and duration of respiratory depression. Therefore, we evaluated the extent and duration of the respiratory depression produced by a single dose of spinal morphine in ten pediatric patients by measuring the minute ventilation ( $V_E$ ) in response to increasing end-tidal carbon dioxide ( $P_{ETCO_2}$ ) concentrations. We assessed the reduction in the slope ( $V_E/P_{ETCO_2}$ ) of this relationship and the shift to the right of the curve, reflected by a reduction in  $V_E$  at  $P_{CO_2}$  60 mmHg ( $V_E$  60), as indices of respiratory depression. Cerebrospinal fluid and plasma levels of morphine were obtained simultaneously with the ventilatory measurements to assess the relationship between respiratory depression and morphine levels.

## Materials and Methods

### Study Population

We studied ten otherwise healthy, ASA physical status 1 or 2 patients (five boys, five girls) undergoing elective surgical repair of craniofacial defects. The mean patient age ( $\pm$  SE) was  $5 \pm 2$  yr, with a range of 4 months–15 yr. Three of the ten patients were less than 1 yr of age, one of whom was younger than 6 months of age. The mean body weight ( $\pm$  SE) was  $15.2 \pm 6.1$  kg, and ranged from 6.2 to 50 kg. No patient received opioids, sedatives, anticonvulsants, or theophylline before surgery. The study protocol was approved by the institutional review board, the Joint Committee on Clinical Investigation. Written informed consent was obtained from each patient's parents, and, when applicable, from the patient, as well.

### Protocol

All patients fasted for at least 4 h before surgery, and were not premedicated. Anesthesia was induced with nitrous oxide, oxygen, and either halothane or isoflurane by mask. With loss of consciousness, an intravenous catheter was placed, 0.1 mg/kg pancuronium was given, and the trachea was intubated with a cuffed endotracheal tube. Anesthesia was maintained with nitrous oxide, oxygen (30%), and either halothane or isoflurane (0–3%). Paralysis was maintained with 0.03

mg  $\cdot$  kg<sup>-1</sup>  $\cdot$  h<sup>-1</sup> pancuronium. Ventilation was controlled to maintain  $P_{aCO_2}$  between 30 and 35 mmHg, as determined by repeated arterial blood gas measurements and by use of an end-tidal gas monitor (Raman Scattering Analyzer, Albion-Ohmeda, Salt Lake City, UT). In addition to routine monitoring devices, a catheter was inserted into a radial artery for determination of blood gases and plasma morphine concentrations. Finally, a 19-G catheter (Becton Dickinson, Sandy, UT; 38-3904-1, epidural catheter) was inserted into the intrathecal space, using a 17-G Tuohy needle, at the L4–L5 interspace, for drainage of cerebrospinal fluid (CSF) during the early phases of the surgical repair. This catheter has an internal volume of approximately 0.1 ml.

Hemodynamic stability and maintenance of adequate blood volumes were achieved by the administration of 5% dextrose in 0.45% saline, infused at maintenance rates calculated according to standard formulae.<sup>9</sup> Third space and blood losses were replaced with lactated Ringers solution and packed red blood cell transfusions.

Approximately 3 h before the conclusion of surgery, 0.02 mg/kg of preservative-free morphine (Duro-morph, Cherry Hill, NJ; 1.0 mg/ml) was administered *via* the intrathecal catheter. Three milliliters of previously withdrawn CSF was injected by barbotage, to eliminate any residual morphine from the catheter. Halothane or isoflurane was discontinued 1 h before the conclusion of surgery, and nitrous oxide was discontinued at the conclusion of surgery.

After completion of surgery, patients were taken to the Pediatric Intensive Care Unit, where neuromuscular blockade was antagonized with 0.07 mg/kg neostigmine and 0.01 mg/kg atropine. To allow a period of time for resolution of facial and pharyngeal swelling, patients' tracheas remained intubated and their lungs mechanically ventilated during the next 18 h. The  $P_{aCO_2}$  was maintained between 35–45 mmHg, and oxyhemoglobin saturation between 95% and 100%, as determined by repeated arterial blood gases and by pulse oximetry (Nellcor, Hayward, CA; N-100). No other sedatives or opioids were given at any time during this study. The assessment of the need for additional analgesia remained under the control of the clinical staff, which did not include the investigators. If a patient had required additional analgesia or sedation, intravenous morphine would have been administered and the patient would have been removed from the study. This did not occur. Patients slept comfortably, and breathed in synchrony with the mechanical ventilator, unless they were dis-

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turbed by tracheal suctioning, repositioning in the bed, or extreme hypercapnia (70–80 mmHg) during re-breathing trials. In general, patients were easily awakened by having their name called. All patients were normothermic during the postoperative study period.

### Ventilatory Measurements

The ventilatory response to inhaled carbon dioxide was determined preoperatively ( $n = 5$ ) and postoperatively at 6 h ( $n = 10$ ), 12 h ( $n = 10$ ), and 18 h ( $n = 8$ ) after intrathecal morphine administration. The patients breathed through a closed circuit in which a pneumotachograph (Hewlett Packard, Andover, MA; 47304A), a side-stream capnograph, and a Hans-Rudolph nonrebreathing valve were placed in series and connected to a rebreathing bag.<sup>10,11</sup> The circuit was primed with 5% CO<sub>2</sub> in oxygen.<sup>12</sup> The volume of the rebreathing bag varied between 2 and 4 l, depending on the size of the patient. The internal volume of the pneumotachograph, capnograph, and nonrebreathing valve combined was 45 ml. The resistance of the pneumotachograph was  $1.1 \text{ cm H}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}^{-1}$  at a gas flow of 1.3 l/s. Tidal volume, respiratory rate, and PETCO<sub>2</sub> were recorded on a Hewlett Packard 7758A, eight-channel recorder running at a paper speed of 10 mm/s. Tidal volume was measured by electronically integrating the flow signal from the pneumotachograph, which was calibrated with a 3-l syringe of air before each measurement. End-tidal carbon dioxide tension was measured with a Puritan-Bennett (Tewksbury, MA; Datex LD 102-27-00) sidestream capnograph that was calibrated before each measurement with 5% CO<sub>2</sub> and air.

Patients breathed either through a face mask that had been sealed with petroleum jelly (preoperative measurements), or through a cuffed endotracheal tube (6, 12, and 18 h measurements). Before obtaining the postoperative measurements, the patients breathed spontaneously at atmospheric pressure for several breaths, to eliminate any hyperinflation that may have occurred during mechanical ventilation. Then patients were allowed to rebreathe 5% CO<sub>2</sub> in oxygen for 3–4 min while maintaining oxyhemoglobin saturation at 95–100%. Because patients sometimes became agitated during marked hypercapnia (PETCO<sub>2</sub> 70–80 mmHg), rebreathing trials were carried out in triplicate at each time point. The best trial, based on absence of agitation, was selected for analysis. Ten minutes of rest were allowed between rebreathing trials at each time point.

### Statistical Analysis

Linear regression analysis of the individual data points for each carbon dioxide response curve yielded the slope ( $V_E/\text{PETCO}_2$ ). The intercept  $V_E$  at PETCO<sub>2</sub> 60 mmHg ( $V_E 60$ ) was calculated from the regression equation. The mean slopes and intercepts for the whole study group were compared preoperatively and at 6, 12, and 18 h after morphine administration by ANOVA for repeated measures and two-tailed  $t$  test with Bonferroni correction. Critical differences between the mean values obtained under different experimental conditions were assessed with the Duncan multiple range test. A  $P$  value  $< 0.05$  was considered significant. Results are expressed as mean  $\pm$  SE.

### Plasma and CSF Morphine Analysis

Samples for plasma and CSF morphine analysis were drawn postoperatively at 6 ( $n = 7$ ), 12 ( $n = 5$ ), and 18 h ( $n = 6$ ) after intrathecal morphine administration, which corresponded to 3, 9, and 15 h after the conclusion of surgery. Samples of CSF were collected after discarding the fluid in the internal volume of the catheter. Blood specimens (3 ml) anticoagulated with heparin were centrifuged immediately. Plasma and CSF samples were then frozen at  $-70^\circ \text{C}$  for analysis by radioimmunoassay (Diagnostic Products, Los Angeles, CA). The assay is accurate to levels of 2 ng/ml, and showed  $< 0.15\%$  cross reactivity with metabolites.

## Results

All of the carbon dioxide response curves were linear, with a mean correlation coefficient ( $r$ ) of  $0.83 \pm 0.02$ . Figures 1–3 demonstrate the mean data at each time point for the entire study group, as well as the individual values before and after morphine administration for all infants and children.

As shown in figure 1,  $V_E/\text{PETCO}_2$  decreased from a preoperative value of  $35.1 \pm 3.7$  to  $16.3 \pm 2.8 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$  ( $1.61 \pm 0.13$  to  $0.31 \pm 0.07 \text{ l} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$ ) 6 h after morphine administration ( $P < 0.01$ ), and remained depressed to  $23.4 \pm 2.9$  and  $23.5 \pm 3.3 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$  ( $0.45 \pm 0.09$  and  $0.48 \pm 0.07 \text{ l} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$ ) at 12 and 18 h, respectively ( $P < 0.01$  compared with control). The  $V_E/\text{PETCO}_2$  for the infants were within the same range as the corresponding values for children, except for a 9-month-old infant, who had the lowest  $V_E/\text{PETCO}_2$  at 6 h.

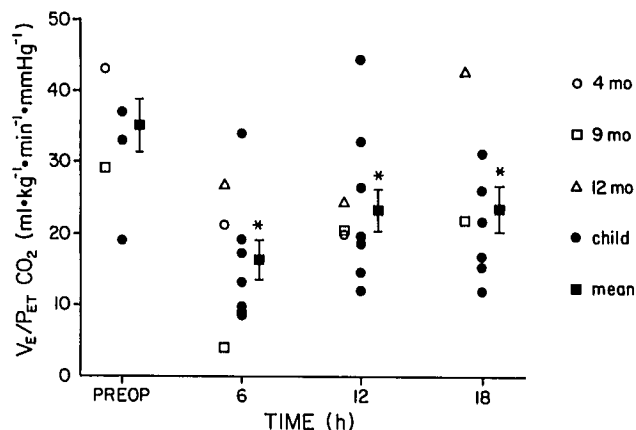


Fig. 1. The carbon dioxide response curve slope ( $V_E/PET_{CO_2}$ ) preoperatively ( $n = 5$ ) and 6 ( $n = 10$ ), 12 ( $n = 10$ ), and 18 h ( $n = 8$ ) after morphine administration in infants (open symbols), children ( $\bullet$ ), and the mean of all patients ( $\blacksquare$ ).  $V_E/PET_{CO_2}$  is reduced at 6, 12, and 18 h after morphine administration compared with the preoperative value. \* $P < 0.05$  compared with preoperative values.

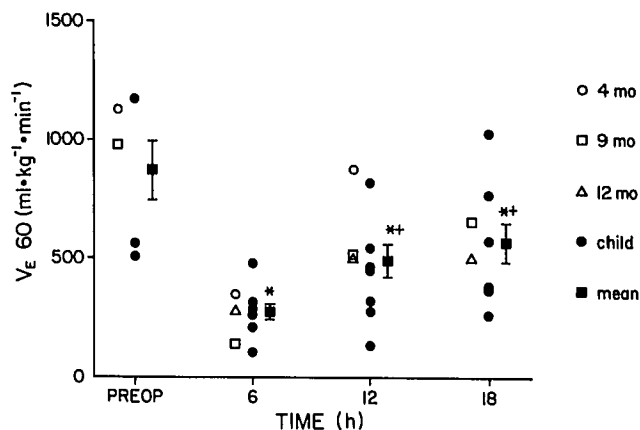


Fig. 2. The minute ventilation at  $PET_{CO_2}$  60 mmHg ( $V_E$  60) preoperatively ( $n = 5$ ) and 6 ( $n = 10$ ), 12 ( $n = 10$ ), and 18 h ( $n = 8$ ) after morphine administration.  $V_E$  60 is reduced at 6, 12, and 18 h compared with the preoperative value, but the 12- and 18-h values are increased compared with the 6-h value. \* $P < 0.05$  compared with preoperative values; + $P < 0.05$  compared with 6-h values.

Figure 2 demonstrates a shift to the right in the ventilatory response curve manifested by a reduction in the mean  $V_E$  60 from a preoperative value of  $874 \pm 125$  to  $276 \pm 32$   $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  ( $12.8 \pm 2.1$  to  $5.5 \pm 1.2$  l/min) at 6 h, with recovery to  $491 \pm 68$  and  $567 \pm 82$   $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  ( $8.5 \pm 1.5$  and  $11.9 \pm 2.0$  l/min) at 12 and 18 h, respectively ( $P < 0.01$  compared with preoperative and 6 h). The  $V_E$  60 did not differ significantly between infants and children.

The changes in CSF morphine concentration over time are shown in figure 3. Mean CSF morphine concentration for the entire study group was  $2,860 \pm 540$  ng/ml at 6 h after morphine administration, and then decreased to  $640 \pm 220$  and  $220 \pm 150$  at 12 and 18 h, respectively ( $P < 0.01$  compared with 6 h). Infants tended to have higher CSF morphine concentrations at 12 and 18 h. However the difference was not statistically significant. Plasma morphine concentrations were less than 2 ng/ml for all patients.

## Discussion

Intrathecal morphine administration in children results in profound and prolonged ventilatory depression, as manifested by a reduction in both the slope ( $V_E/PET_{CO_2}$ ) and the intercept ( $V_E$  60) of the ventilatory response curve to carbon dioxide. The reduction in  $V_E/PET_{CO_2}$  and in  $V_E$  60 is greatest 6 h after morphine administration, and only partially recovers 12 and 18 h later.

Infants (4–12 months of age) were not more susceptible to respiratory depression than children ( $> 12$  months of age). Reductions in  $V_E/PET_{CO_2}$  and  $V_E$  60 in our study were associated with elevated CSF morphine concentrations.

There are few reports of the ventilatory response to carbon dioxide in children<sup>13,14</sup> or adults<sup>15</sup> after spinal or epidural opioid administration. These studies have yielded preoperative carbon dioxide response curve slopes  $V_E/PET_{CO_2}$  of  $1.51 \pm 0.72$ <sup>13</sup> and  $1.68 \pm 0.12$ <sup>14</sup>

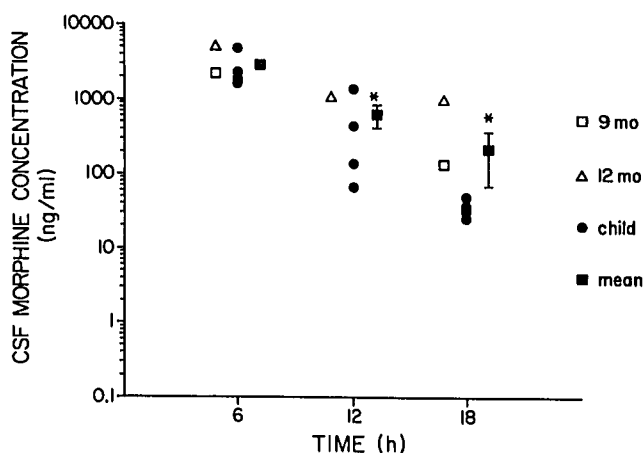


Fig. 3. The CSF morphine concentration at 6 ( $n = 7$ ), 12 ( $n = 5$ ), and 18 h ( $n = 6$ ) after morphine administration. The highest CSF morphine concentrations were sampled 6 h after morphine administration, and fell exponentially at 12 and 18 h. \* $P < 0.05$  compared with 6-h values.

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$1 \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$ , which agree well with our preoperative slope of  $1.61 \pm 0.13 \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$ . Attia *et al.*<sup>13</sup> noted a fall in both  $V_E/\text{PET}_{\text{CO}_2}$  and  $V_E$  at  $P_{\text{CO}_2}$  55 mmHg after epidural morphine administration (0.05 mg/kg) in which the depression in slope persisted for 22 h, and the depression in  $V_E$  at  $P_{\text{CO}_2}$  55 mmHg persisted for 10 h. Our ventilatory drive data are consistent with these findings, and show more prolonged depression in slope than in the intercept of the carbon dioxide response curve. We made no attempt to assess resting  $V_E$  and  $\text{Pa}_{\text{CO}_2}$ , because our patients' lungs were mechanically ventilated to maintain normocapnia and hemoglobin oxygen saturation of 95–100% between the carbon dioxide rebreathing trials.

The ventilatory depression that occurs after intrathecal morphine administration appears to result from the rostral spread of morphine in the CSF, rather than by systemic absorption. Plasma morphine concentrations were always less than the limits of detection with our assay ( $< 2 \text{ ng/ml}$ ). With our experimental model, it was not possible for us to directly determine the extent of mixing of morphine in the CSF, and it is possible that the cephalad spread of morphine was variable from patient to patient. Directional changes in ventilatory effects were consistent with directional changes in CSF morphine concentrations. However, Gourlay *et al.*<sup>16</sup> showed that lumbar intrathecal morphine reaches the brain by bulk flow of CSF. Consistent with our data, Gregory *et al.*<sup>17</sup> found maximal medullary concentrations of tritiated morphine associated with maximal ventilatory depression 6 h after lumbar intrathecal injection. Additionally, patients tolerated endotracheal intubation after intrathecal morphine administration without the need for supplemental analgesia. This indicates that morphine reached the brain after intrathecal injection.

Our use of an intrathecal sampling catheter probably disturbed the kinetics less than repeated lumbar punctures, each of which can cause leakage of CSF. In addition, to prevent unnecessary interference with CSF dynamics, the size of each CSF sample was minimized and kept constant. Theoretically, sampling through the same catheter through which morphine was administered may lead to serious contamination of the samples. We attempted to minimize this risk by injecting 3 ml of CSF through the catheter after the initial morphine injection, and by discarding the internal volume of the intrathecal catheter before each sample was obtained. The ventilatory depressant effects of intrathecal morphine occurred in the face of variable CSF morphine concentrations. It is conceivable that ventilatory

depression could be produced by a very large range of CSF morphine concentrations among individuals, because there is a very large range of tolerated and effective opiate doses in clinical use, which may not be explained fully by changes in morphine disposition. Others have noted large interindividual variability in morphine CSF pharmacokinetics.<sup>18</sup>

Spinal opioid administration bypasses the blood and directly places an agonist into the CSF, which bathes the receptor sites in the spinal cord (substantia gelatinosa) and brain. This study confirms that intrathecal injection of small doses of morphine results in CSF concentrations that are orders of magnitude greater than those observed after parenteral morphine administration.<sup>19–21</sup> Although our study was not designed to assess the efficacy of the analgesia obtained when using intrathecal morphine, these very high levels may explain, in part, the ability of spinally administered opiates to achieve analgesia in very low doses. Furthermore, throughout this study, plasma morphine levels were undetectable. Others have also noted very low plasma morphine levels after intrathecal administration.<sup>18,22,23</sup> Thus, the analgesia or ventilatory depression achieved after intrathecal opioid administration cannot be related to the systemic absorption of morphine.

It is unlikely that other factors were the predominant reason for ventilatory depression. On departure from the operating room, all patients had end-tidal anesthetic gas concentrations of  $< 0.1\%$ , and the first measurement occurred 3 h later (6 h after morphine administration). Knill and Gelb<sup>24</sup> showed that 0.1-MAC halothane sedation did not affect the ventilatory response to hypercarbia. It is, therefore, unlikely that residual effects of anesthetic gas contributed to ventilatory depression during carbon dioxide rebreathing trials. Similarly, it is unlikely that the surgical procedure *per se* contributed to ventilatory depression, because there were no chest wall incisions that may have caused splinting.

The preoperative measurements of the ventilatory response to carbon dioxide rebreathing were performed with a face mask on the patient, whereas the patient breathed *via* endotracheal tube during the postoperative measurements. Askanazi *et al.* compared the use of a face mask to a canopy system during carbon dioxide rebreathing, and found larger tidal volumes when the face mask was used.<sup>25</sup> Our preoperative measurement through a face mask cannot be considered a true control for the postoperative measurements through an endotracheal tube. A true control preoperative ventilatory measurement would involve endotracheal tube place-

ment in unsedated children, and would be ethically indefensible, in our opinion. The preoperative measurement was obtained to provide a point of comparison with other studies, and our preoperative data are in good agreement with the two previously published studies in children.<sup>13,14</sup> It is possible that there was greater resistance to breathing during the postoperative measurements (6–18 h), which may have contributed to the reduction in  $V_E/PET_{CO_2}$  and  $V_E 60$ . This may also explain, in part, the fact that our values for  $V_E/PET_{CO_2}$  after morphine administration were lower than those reported by Attia *et al.*<sup>13</sup> However, endotracheal tube resistance was not limiting, because  $V_E 60$  increased at 12 and 18 h compared with the 6-h value.

Some studies raised the concern that newborns and infants may be more susceptible to respiratory depression after opioids than are older patients.<sup>6–8</sup> Conversely, Hertzka *et al.*<sup>26</sup> found no exaggerated respiratory depression in infants as young as 3 months. Our data agree with the latter report. We found similar degrees of ventilatory depression over a wide range of ages from 4 months to 15 yr. The similarity of  $V_E/PET_{CO_2}$  and  $V_E 60$  in pediatric patients of various ages correlated with the similarity in CSF morphine levels in patients of various ages.

In conclusion, intrathecal morphine administration causes profound and prolonged ventilatory depression, as determined by a reduction in the slope ( $V_E/PET_{CO_2}$ ) of the carbon dioxide response curve, and by a shift to the right of this curve, as reflected by a reduction in  $V_E$  at  $P_{CO_2} 60$  mmHg ( $V_E 60$ ). Furthermore, this ventilatory depression results from persistently increased CSF morphine levels, and may result from rostral spread of morphine in the CSF, rather than from systemic absorption. Therefore, patients treated with intrathecal morphine require a regular system of monitoring for respiratory depression during the first 18 h after a single dose. However, infants over 4 months of age do not appear to be more vulnerable than older children.

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