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Dose-Response Pharmacology of Intrathecal Morphine in Human Volunteers

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Background: **Intrathecal morphine sulfate (ITMS) administration was introduced into clinical practice in 1979. Inadequate information exists delineating ITMS respiratory effects in the dosage range most frequently employed today. This study evaluated 0.2, 0.4, and 0.6 mg ITMS in male volunteers.**

Methods: **Twenty healthy, young, adult male volunteers received 0.0, 0.2, 0.4, or 0.6 mg preservative-free ITMS in an isobaric solution administered at the L3–L4 interspace in a double-blind randomized fashion. Respiratory function was assessed by finger pulse oximetry (Sp_{O_2}), respiratory rate, and arterial blood gas analysis *via* an indwelling arterial catheter and the slope of the ventilatory response to carbon dioxide (V_E/CO_2). Analgesia was assessed by the effect of ITMS on moderate pain produced by pressure algometry at the tibia. The need for supplemental oxygen, 2 L/min *via* nasal cannulae, was determined by the failure of verbal and tactile prompts to maintain subjects' $Sp_{O_2} \geq 85\%$ on more than two occasions. Heart rate, arterial blood pressure, sedation level, pupil size, and the incidence of adverse effects also were documented. All the above measurements were made before and 30 min after ITMS, hourly for 11 h, and then every 2 h for 12 more h.**

Results: **ITMS produced significant dose-related decreases in Sp_{O_2}. Mild desaturations ($Sp_{O_2} \geq 85$ and $< 90\%$) occurred in 2 of 5, 3 of 5, and 4 of 5 subjects receiving 0.2, 0.4, and 0.6 mg ITMS, respectively. Moderate to severe desaturations ($Sp_{O_2} < 85\%$) occurred in 0 of 5, 2 of 5, and 4 of 5 subjects receiving 0.2, 0.4, and 0.6 mg ITMS, respectively. The need for supplemental oxygen also was significantly related to ITMS dose, with 0 of 5, 1 of 5, and 4 of 5 subjects requiring oxygen after 0.2, 0.4, and 0.6 mg ITMS, respectively. Nasal oxygen administration consistently alleviated hypoxemia. Increases in arterial carbon dioxide tension (Pa_{CO_2}) and decreases in *p*H were significantly related to ITMS dose. Peak mean Pa_{CO_2}s were 42.4, 44.9, and 50.7 mmHg in the 0.2-, 0.4-, and 0.6-mg groups, respectively. These peaks occurred 6.5–7.5 h after ITMS injection. ITMS produced significant dose-related depression of V_E/CO_2. Maximum mean depressions of V_E/CO_2 were to 61%, 63%, and 32% of baseline in the 0.2-, 0.4-, and 0.6-mg groups, respectively. These nadirs occurred 3.5–7.5 h after ITMS injection. Some subjects receiving 0.6 mg ITMS experienced profound (<20% of baseline) and prolonged (<50% of baseline for up to 20 h) V_E/CO_2 depression. Magnitude and duration of analgesia after ITMS were dose-related. Changes in heart rate, systolic blood pressure, and respiratory rate were not significantly related to ITMS dose. Hypoxemia was not related to respiratory rate. Although ITMS produced statistically significant dose-related increases in sedation and decreases in pupil size, these changes were small and did not coincide with hypoxemia. ITMS caused dose-related increases in emesis, but the severity of pruritus and urinary retention was unrelated to dose.**

Conclusion: **ITMS produced dose-related analgesia and respiratory depression in nonsurgical healthy, young, adult male volunteers. Respiratory depression was significant after 0.2 or 0.4 mg and profound and prolonged after 0.6 mg. No clinical signs or symptoms, including respiratory rate, reliably indicated hypoxemia. Pulse oximetry reliably detected hypoxemia after ITMS, and supplemental nasal oxygen (2 L/min) effectively corrected this hypoxemia. (Key words: Analgesics, opioid: morphine. Anesthetic technique: intrathecal morphine. Complications: hypoxemia; respiratory depression. Monitoring: pulse oximetry; respiratory rate; sedation. Pain: experimental. Ventilation: carbon dioxide response.**

SINCE its introduction to clinical practice in 1979,[1] the application of intrathecal opioids, and particularly intrathecal morphine sulfate (ITMS), has gained significant acceptance.[2–4] Nevertheless, it is likely that this pain control modality remains underutilized.[4,5] The most common reasons and justifications given for restricting the application of intrathecal opioid pain relief are the risk of respiratory depression[3,4] and the complexity and cost of monitoring for this potentially disastrous complication.[6] While the analgesia provided by ITMS is arguably superior to that by even epidural morphine,[2] the incidence of significant respiratory depression is also greater.[4]

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Initially after clinical introduction, ITMS doses were high by current standards and ranged from 0.5 to 20 mg, with 0.5–2.0 mg the most frequently employed.[2] More recent clinical studies suggest that ITMS doses less than 0.2 mg may be optimal, at least after certain abdominal surgeries.[7,8] Most frequently, ITMS doses of 0.2–1.0 mg are being clinically applied.[3,4] Few data exist delineating dose-response ITMS respiratory actions in this dose range. In addition, key issues of safety and efficacy remain inadequately addressed, as they were in 1984.[2,3] We designed this human volunteer investigation to describe the dose-response pharmacologic profile of ITMS. Doses were chosen that were judged to be most relevant to clinical practice based on our experiences and published recommendations.[2–4] We were interested particularly in determining the time course and magnitude of ITMS effects on ventilation and oxygenation and the reliability of indicators of ITMS-induced respiratory depression.

Methods and Materials

Approval for the investigation was obtained from the Institutional Review Board of the University of Utah Health Sciences Center. Oral and written informed consent was obtained from paid volunteers solicited from outside the department of anesthesia. Inclusion criteria required volunteers to be nonsmoking, healthy men between the ages of 18 and 45 yr. Volunteers had to weigh within 20% of their ideal body weight. They had to require no routine medications, have no history of drug abuse, and agree to refrain from caffeinated drinks and alcohol consumption for 48 h prior to the study. Volunteers were subjected to trial carbon dioxide challenges and experimental algometry to familiarize them with these tests before beginning the investigation. All studies were performed in the anesthesia clinical research area. Studies began at 7 AM. Intravenous access was secured with an 18- or 20-G plastic catheter after local anesthesia with 0.5 ml 0.5% lidocaine. Lactated Ringer's solution was infused with a McGaw AccuPro pump (American Edwards Laboratories, Irvine, CA) at 40 ml/h. After local anesthesia with 1.0 ml 0.5% lidocaine, radial artery cannulation with a 2-in, 20-G plastic catheter was performed for continuous monitoring of blood pressure (Tektronix, Beaverton, OR) and intermittent sampling for blood gas and *p*H analysis (NOVA STAT profile 4, Waltham, MA). Three leads for electrocardiogram (Tektronix) monitoring of heart rate (HR) then were applied.

Respiratory Assessments

Oxygen saturation (Sp_{O_2}) was monitored continuously by transcutaneous finger pulse oximetry (Nelcor, Hayward, CA). The audible component of the monitor was silenced to avoid the possibility of changes in this signal associated with desaturations stimulating subjects. The low saturation limit alarm was set at 85%, and its audible component was left active. Respiratory rate (RR) was measured by counting breaths visually over 60 s with the volunteers in a quiet, undisturbed state at intervals described below and during oxyhemoglobin desaturation episodes. Apnea was considered present if a spontaneous respiration was not initiated over 15 s. $Sp_{O_2} < 90\%$ but $\geq 85\%$ was considered to represent mild desaturation and not treated. $Sp_{O_2} < 85\%$ was considered to represent moderate desaturation and intervention by verbal, and if needed, tactile stimulation was made to restore Sp_{O_2} to $\geq 85\%$. For safety reasons, once three Sp_{O_2} episodes of < 85% occurred, oxygen, 2 L/min *via* nasal cannula, was administered continuously for the remainder of the experiment.

We used a modified Read rebreathing circuit as previously described.[9,10] The rebreathing apparatus had a 7.5-1 neoprene rebreathing bag enclosed in a Lucite box; to measure ventilatory flow, a Validyne (Northridge, CA) differential pressure transducer measured the pressure difference across a Fleisch (Switzerland) pneumotachograph at the outlet of the box. Flow was directed either into the bag or through the pneumotachograph by a three-way valve located at the mouth of the box, permitting the subject to breathe directly into the room when not rebreathing carbon dioxide. Inspiratory and expiratory limbs of the circuit were separated by a Hans-Rudolph valve. Carbon dioxide concentration was measured by an infrared carbon dioxide analyzer (Lifespan 100, Biochem International, Waukesha, WI), which sampled gas at the mouthpiece at a rate of 200 ml/min and returned it to the central chamber of the Hans-Rudolph valve. The carbon dioxide analyzer was calibrated with three different gas concentrations: 0, 5.0%, and 10%. Inspiratory circuit resistance was no more than 1.9 $cmH_2O \cdot l^{-1} \cdot s$, and expiratory circuit resistance was no more than 1.7 $cmH_2O \cdot l^{-1} \cdot s$ between flow rates of 15 and 135 L/min.

Flow, pressure, and carbon dioxide signals were sampled at a rate of 100 Hz by a microcomputer (Samsung XTC 8088, Taiwan) 12-bit analog to digital (A/D) converter (Data Translations, Marlborough, MA). Inspiratory mouth occlusion pressure (PO.1) measurements

were made at the start of every inspiration. The inspiratory occlusion valve was closed 300 ms after the start of expiration. If the shape of the occluded pressure waveform was satisfactory, inspiration pressure was sampled and stored. A signal to reopen the valve was sent 120 ms after the onset of inspiration.

After the subject was allowed to breathe quietly through the mouthpiece with the nose clip in place, the three-way valve was switched to the rebreathing bag previously filled with 7.0% CO_2 and 93.0% O_2. For each breath, the following data were displayed on the video terminal and stored electronically: inspiratory time (T_I); breath duration (T_{TOT}); fractional inspired carbon dioxide concentration and end-tidal carbon dioxide concentration ($P_{ET_{CO_2}}$); tidal volume (V_T); minute ventilation (V_E); P0.1; and time elapsed since the start of carbon dioxide rebreathing. All gas volumes were corrected to body temperature pressure saturated. Subjects were encouraged to rebreathe as long as possible but were permitted to stop at any time. The desired goal was to reach a $P_{ET_{CO_2}}$ of 65 mmHg. The increase in $P_{ET_{CO_2}}$ during carbon dioxide rebreathing tests was always at least 15 mmHg, but not more than 25 mmHg.

After completion of each carbon dioxide challenge, plots of V_E *versus* $P_{ET_{CO_2}}$ and PO.1 *versus* $P_{ET_{CO_2}}$ were displayed on the video display terminal. To ensure that the regression line reflected only data from the linear portion of ventilatory response, data from the first 10 breaths were excluded from analysis. Data from all other breaths were used for least-squares linear regression. The slope of the ventilatory response to carbon dioxide (V_E/CO_2, $L \cdot min^{-1} \cdot mmHg^{-1}$), and the slope of the occlusion pressure response to carbon dioxide ($P0.1/CO_2$, $cmH_2O/mmHg$), were the variables chosen to depict each subject's response to carbon dioxide.

Arterial carbon dioxide tension and end-tidal carbon dioxide tension measurements were used to assess resting ventilatory depression. $P_{ET_{CO_2}}$ measurements were made before carbon dioxide challenges with nose clips applied and subjects fully expiring into a 30-cm-long tube with expired gas sampled *via* a proximal side port at a rate of 200 ml/min. The highest $P_{ET_{CO_2}}$ during this maneuver was documented as the end-tidal carbon dioxide tension.

Analgesic Assessment

The analgesic effects of ITMS were assessed by pressure algometry at the tibia.[11] A device that was stable but comfortable was built that permitted the application of a metal plunger to the skin at mid-tibia (fig. 1). The plunger had a flat circular surface, 1 cm in diameter. Plunger pressure was increased in 1-PSI increments from 0 PSI every 2 s until pressures producing mild and moderate pain (rated at 2 and 5, respectively, of 10 on 0–10 pain scale) were produced. The device was removed in between assessments.

Other Effects

Sedation level was scored on a 0–3 scale (0 = awake, spontaneously conversant; 1 = awake, not spontaneously conversant; 2 = asleep, easily aroused; 3 = asleep, difficult to arouse). Pupil size was measured in millimeters with a standard pupillometer with dim

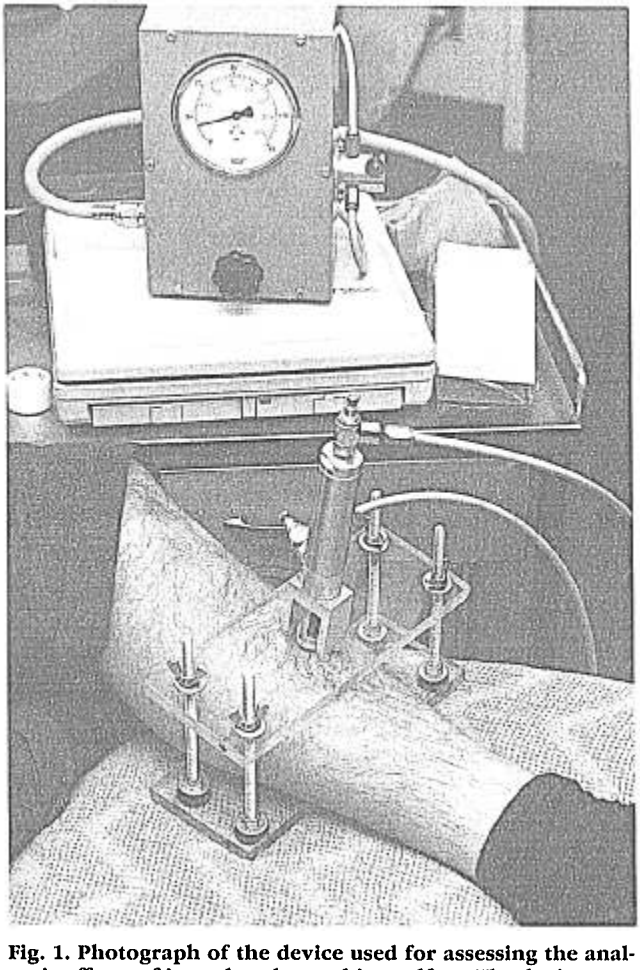

Fig. 1. Photograph of the device used for assessing the analgesic effects of intrathecal morphine sulfate. The device contained two Plexiglas plates that could be screwed down firmly, but comfortably, so as to stabilize the housing unit containing a pneumatically controlled metal plunger. The metal plunger could be applied to the tibia with a force determined by the manual manipulation of a gauge controlling the delivered air pressure.

room lights kept at a constant intensity throughout the day.

The incidence and time of onset of pruritus, vomiting, and the need for antiemetic therapy were noted. Metoclopramide (10 mg, intravenous), was administered if emesis was severe (persistent) or repeated (six or more episodes). The incidence of urinary retention and the need for bladder catheterization to relieve symptoms as noted and requested by the subject, respectively, also were documented.

Intrathecal Morphine

Sterile, preservative-free, isobaric 2-ml solutions containing 0.0, 0.2, 0.4, or 0.6 mg morphine were prepared by the hospital pharmacy according to a blocked randomization table for 20 subjects. The study design of five subjects in each dose group was chosen after consultation with our statistician. Investigators and subjects were blinded to study solution morphine content. After being placed in the lateral position, the skin surrounding the lumbar area was prepared with a betadine solution and draped. After local anesthesia with 1% lidocaine, 1–2 ml at the L3–L4 interspace, a 25-G Whitaker needle was introduced until cerebrospinal fluid (CSF) could be aspirated. Study solution was aspirated under sterile conditions into a 10-ml syringe, which was attached to the spinal needle, and an additional 1 ml of CSF was aspirated. Then, the entire syringe contents was injected into the subarachnoid space over 15–30 s. Verification of the ability to aspirate CSF was made after solution injection. The subject was immediately placed in the supine position with the head and back 5–10 degrees up from the horizontal position.

Subjects were encouraged to remain in the supine position except to go to the bathroom or to eat. Lunches and dinners, standardized for caloric as well as protein, carbohydrate, and fat content, were supplied by the hospital dietary service. A faculty anesthesiologist or 3rd-yr anesthesiology resident was present at all times during the study.

Assessment Intervals and Order

All measurements were made before intrathecal morphine and 30 min after ITMS. Measurements were repeated every hour thereafter for 11 h, then every 2 h for an additional 12 h. All measurements that could be made without disturbing subjects (HR, systolic and diastolic blood pressures, Sp_{O_2}, RR, and sedation level) were made first. Following this, arterial blood gas samples were obtained expeditiously to minimize the impact of making assessments that could stimulate ventilation.

Statistics

Demographic variables (age, height, and weight) were compared by one-way analysis of variance. To normalize continuous response variables (systolic blood pressure, HR, RR, *p*H, arterial carbon dioxide tension [Pa_{CO_2}], V_E/CO_2, $P0.1/CO_2$, algometry, and pupil diameter) for differences in baseline starting values, each variable was transformed by taking the difference from baseline. These transformed variables were compared for linear dose effects, time changes after administration, and dose-time interactions by repeated measures multivariate analysis of variance using restricted maximum likelihood estimation. A factor analytic covariance structure minimized the Akaike's information criterion. As sedation scores *versus* dose were r by c tables with ordered categories, they were analyzed by the Γ statistic with statistical significance determined by approximate *t*-tests using asymptotic standard errors. Statistical software was the 1D, 4F, and 5V modules of BMDP (BMDP Statistical Software, Los Angeles, CA). Plots of continuous variables used original variables, not the transformed variables used for analysis; because of excessive overlapping, error bars were not included in the plots. A trend test (Cochran armitage test) was used to determine whether the incidence of oxyhemoglobin desaturations, low RR, the need of oxygen therapy, pruritus, emesis, the need for antiemetic therapy, urinary retention, and the need for bladder catheterization had statistically significant ordering based on dose. Values are expressed as mean ± SEM unless otherwise specified. Statistical significance was achieved if $P < 0.05$.

Results

Twenty-one subjects were enrolled in the investigation because replacement of the fourth subject was required. This subject tolerated lumbar puncture and intrathecal injection poorly. He moved during ITMS injection, and it was unclear whether there was complete solution delivery into the subarachnoid space. All enrolled subjects completed the study. The age, weight, and height of the subjects were 25.4 ± .64 yr, 75.4 ± 2.0 kg, and 180.3 ± 1.1 cm, respectively, with no significant intergroup differences. Baseline values for HR and systolic blood pressure were 62.9 ± 2.2 beats/min and 130.4 ± 3.0 mmHg, respectively. No statistically significant ITMS dose-related HR or systolic blood pres-

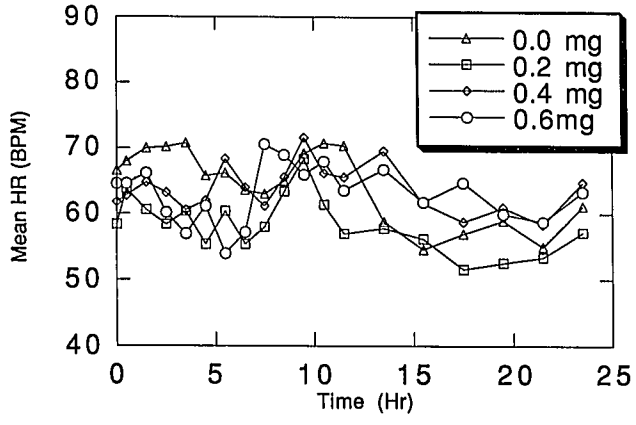

Fig. 2. Mean heart rate *versus* time before (time 0) and hours after intrathecal morphine sulfate by dosage group.

sure effects were detected. No arrhythmias, besides bradycardia, which occurred at times in all groups, were observed. There were significant changes over time for HR (fig. 2) and systolic blood pressure (fig. 3) in all groups.

Respiratory Assessments

Baseline RRs were 14.5 ± 0.6 breaths/min. ITMS dose-related effects on RR were not statistically significant (fig. 4). No statistically significant time-related effect on RR was detected in any dose group. No apnea was observed, and only four subjects experienced RRs of 8 or lower (table 1). There was no statistically significant relationship between these slow RRs and dose. No subject experienced an RR lower than 7. Baseline

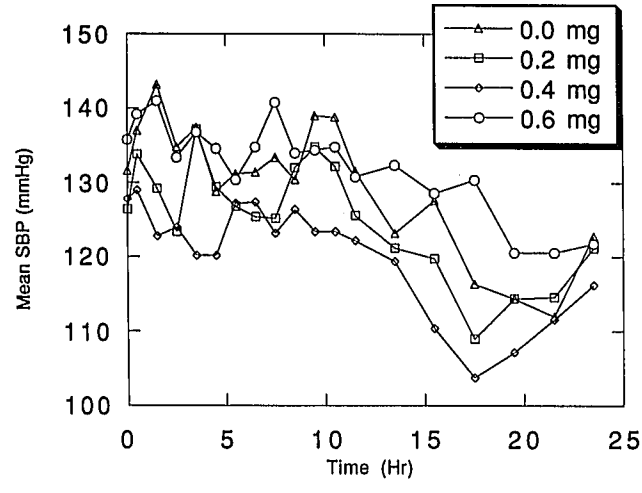

Fig. 3. Mean systolic arterial blood pressure *versus* time before (time 0) and hours after intrathecal morphine sulfate by dosage group.

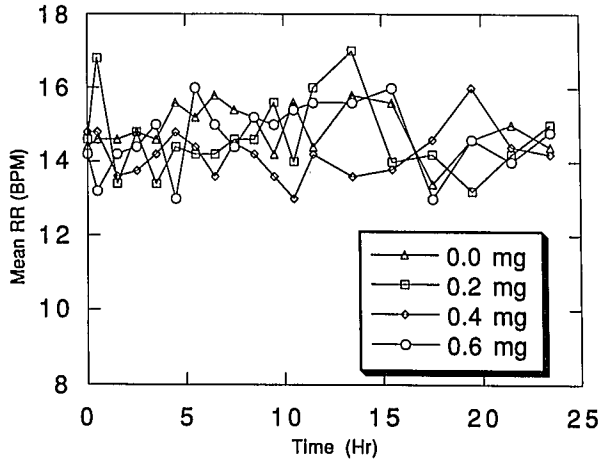

Fig. 4. Mean respiratory rate *versus* time before (time 0) and hours after intrathecal morphine sulfate by dosage group.

Sp_{O_2}s were 97.5 ± 0.4%. The incidence of oxyhemoglobin desaturations was related to ITMS dose in a statistically significant fashion (table 1). $Sp_{O_2} < 90$ but ≥ 85% occurred in two subjects receiving 0.2 mg ITMS, though only once briefly in one subject and three times in the other. All three desaturation episodes in the latter subject were associated with television watching. Two and four subjects receiving 0.4 and 0.6 mg ITMS, respectively, experienced $Sp_{O_2} < 85\%$ (table 1). Two subjects, one in the 0.4- and one in the 0.6-mg ITMS group experienced Sp_{O_2}s < 80% before the application of supplemental oxygen. These and most other oxyhemoglobin desaturations occurred in awake subjects breathing at normal RRs but with clinically apparent shallow tidal volumes. The need for supplemental oxygen *via* nasal cannulae also was related to dose in a statistically significant fashion (table 1). Hypoxemia consistently was corrected by the application of supplemental oxygen.

Table 1. Percent (and Number) of Subjects by ITMS Dose Experiencing One or More Episodes of Sp_{O_2} <90 and <85%, RR ≤ 8 and Requiring Supplemental Oxygen

ITMS Dose (mg)	Sp_{O_2} <90%*	Sp_{O_2} <85%*	RR 7–8	Supplemental Oxygen Needed*
0	0 (0)	0 (0)	0 (0)	0 (0)
0.2	40 (2)	0 (0)	40 (2)	0 (0)
0.4	60 (3)	40 (2)	20 (1)	20 (1)
0.6	80 (4)	80 (4)	20 (1)	80 (4)

* $P < 0.05$; see text for explanation.

ITMS = intrathecal morphine sulfate; RR = respiratory rate; Sp_{O_2} = oxyhemoglobin saturation.

Baseline Pa_{CO_2} and *p*H values were 37.1 ± 0.5 mmHg and 7.42 ± 0.005, respectively. A statistically significant dose-related increase in Pa_{CO_2} and decrease in *p*H was detected after ITMS (figs. 5 and 6). Significant time-related effects also were noted for Pa_{CO_2} and *p*H in all groups (figs. 5 and 6). First peak Pa_{CO_2}s were 42.4, 44.9, and 50.7 mmHg in the 0.2, 0.4, and 0.6 groups, respectively. These peaks occurred 6.5–7.5 h after ITMS injection. Second peaks in Pa_{CO_2} occurred in a fashion consistent with the significant time effect observed on all groups (fig. 5). The highest individual Pa_{CO_2} observed was 55.8 mmHg. Baseline $P_{ET}CO_2$ was 36.2 ± 0.6. No statistically significant relationship between ITMS dose and $P_{ET}CO_2$ was found.

Baseline slopes of the ventilatory response to carbon dioxide were 2.76 ± 0.29 $L \cdot min^{-1} \cdot mmHg^{-1}$. A statistically significant ITMS dose-related depression of the slope of the ventilatory response to carbon dioxide was observed (fig. 7). Maximum depression of the slope of the ventilatory response to carbon dioxide, expressed as a percent of the mean baseline measurement was to 61%, 63%, and 32% for the 0.2-, 0.4-, and 0.6-mg ITMS groups, respectively. The time to these peak effects was 3.5, 7.5, and 5.5 h, respectively. However, the mean slope of the ventilatory response to carbon dioxide in subjects receiving 0.6 mg ITMS was still <50% of baseline 19.5 h after ITMS injection. At times, individual subjects in this highest dose group had their response depressed to less than 20% of baseline. In subjects with this degree of depression, little to no stimulation or arousal occurred during rebreathing challenges, even at end-tidal carbon dioxide tensions of 70–75 mmHg. While the 0.2- and 0.4-mg ITMS dose groups generally regained carbon dioxide responsiveness faster (fig. 7), great inter- and intraindividual variability existed. Baseline slopes of the occlusion pressure response to carbon dioxide were 0.41 ± 0.08 $cmH_2O/mmHg$. Statistically significant dose-related effects on the occlusion pressure response to carbon dioxide were present and similar to ITMS effects on the ventilatory response to carbon dioxide. A statistically significant time effect on all ITMS dose groups was observed for both the ventilatory and occlusion pressure responses to carbon dioxide.

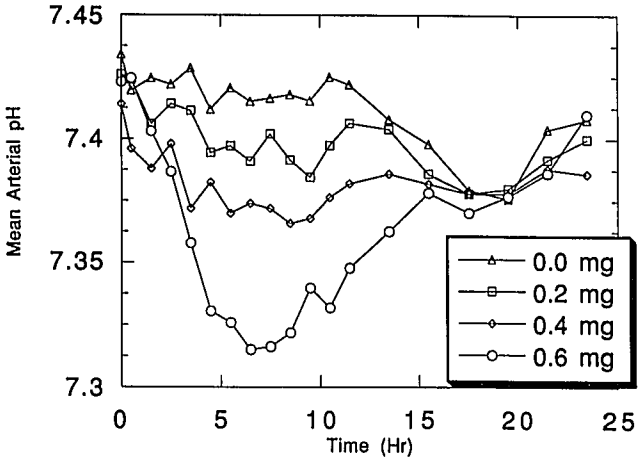

Fig. 6. Mean arterial *p*H *versus* time before (time 0) and hours after intrathecal morphine sulfate by dosage group.

Analgesic Assessment

Because of technical problems, pressure algometry was not performed in four subjects (1 in 0.0-, 1 in 0.2-,

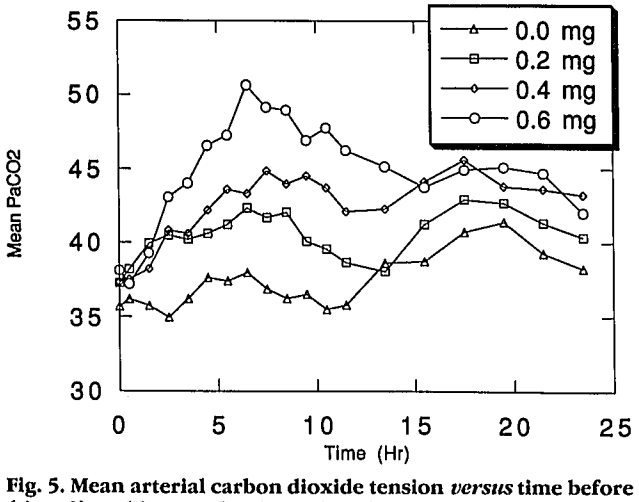

Fig. 5. Mean arterial carbon dioxide tension *versus* time before (time 0) and hours after intrathecal morphine sulfate by dosage group.

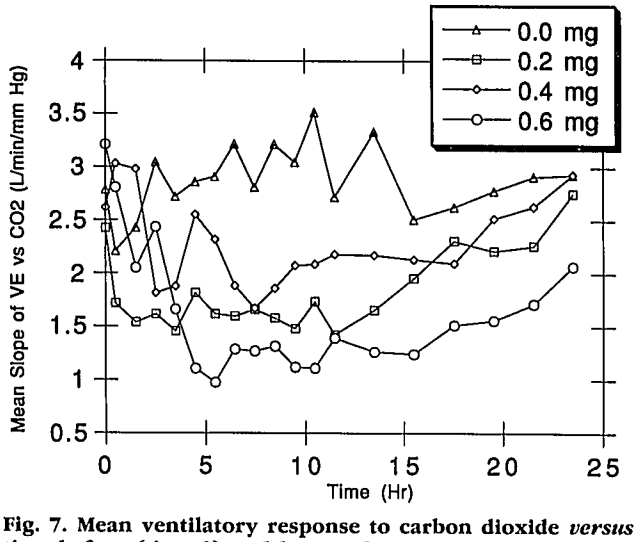

Fig. 7. Mean ventilatory response to carbon dioxide *versus* time before (time 0) and hours after intrathecal morphine sulfate by dosage group.

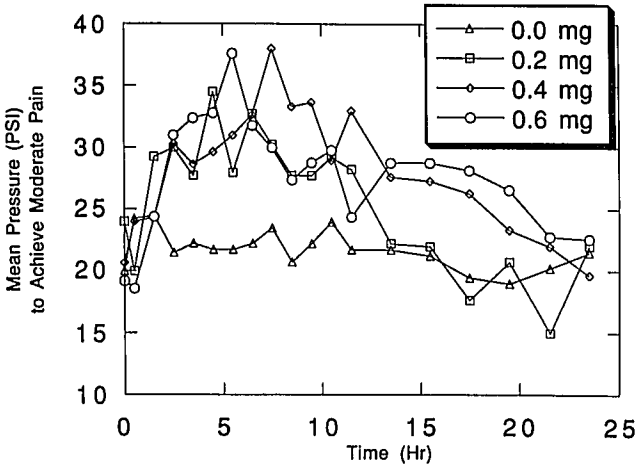

Fig. 8. Mean moderate pain score *versus* time before (time 0) and hours after intrathecal morphine sulfate by dosage group.

and 2 in 0.4-mg ITMS dose groups). Baseline pressure values assessed as moderate pain were 20.9 ± 1.1 PSI. Statistically significant dose-related analgesic effects were found (fig. 8). Maximum pressures judged as moderately painful were 144%, 184%, and 196% of baseline in the 0.2-, 0.4-, and 0.6-mg groups, respectively. These peak analgesic effects occurred 4–7 h after ITMS injection (fig. 8). The effects of time on all groups were also statistically significant.

Other Effects

Sedation scores were 0 for all subjects at baseline. Sedation scores were related to ITMS dose in a statistically significant fashion only from 4.5 to 11.5 h after ITMS. Increases in sedation did not consistently precede or coincide with hypoxemia. Most often, subjects were awake (sedation score 0 or 1) when oxyhemoglobin desaturations occurred. Baseline pupil diameter was 4.5 ± 0.2 mm. The relationship between ITMS dose and pupil size was also statistically significant. However, pupil diameter changes were very small, most often only 1–2 mm, and did not consistently precede or coincide with hypoxemia.

Pruritus occurred in all subjects receiving ITMS. It was most often the first symptom noted and usually occurred within 1–3 h of drug administration. No pruritus occurred in subjects dosed with placebo. Emesis was ITMS dose-related in a statistically significant fashion, but the need for antiemetic therapy was not (table 2). Urinary retention and the need for bladder catheterization was also not related to ITMS dose in a statistically significant manner (table 2). No subject experienced spinal headache or reactivation of a herpes virus infection after the study.

Discussion

Initial reports of intrathecal morphine in humans suggested that this route of opioid administration could result in analgesia with little or no respiratory depression.[1,12] This was the case in these reports even after ITMS doses of 0.5 or 1.0[1] and 20 mg.[12] It would later be recognized that certain factors in those studies, such as opioid tolerance in cancer patients[1] or the use of ITMS in a hyperbaric solution and a 40 degree head-up position,[12] had prevented greater degrees of respiratory depression from occurring. Other early reports of ITMS administration in acute pain settings (where opioid tolerance was unlikely) also employed doses that are now considered to be relatively high with noting only occasional clinically significant respiratory depression. Doses in these reports were most frequently in the 0.5–2.0-mg range but were as high as 5 mg.[2,3,13] Even in the obstetric patient population ITMS doses of 1.0–2.0 mg were employed for relief of labor pain.[14] Additional reports eventually highlighted the real potential for severe and/or delayed respiratory depression after ITMS.[15–17]

More recently studies have evaluated ITMS doses of 0.04–0.25 mg, and doses of 0.1–0.2 mg have been recommended.[7,8,18,19] Others have suggested and reports confirm that intermediate doses of ITMS (0.3–1.0 mg) are perhaps most appropriate. In fact, to date, though several dose-response studies exist,[7,8,13,18,20–22,#,**] only two of these reports[21,22] evaluated more than one dose within the range of 0.2–0.8 mg that is now considered to be most often appropriate for postoperative analgesia.

Table 2. Percent (and Number) of Subjects by ITMS Dose Experiencing at Least One Episode of Emesis and Urinary Retention and Requiring Antiemetics or Urinary Bladder Catheterization

ITMS Dose (mg)	Emesis*	Urinary Retention	Antiemetics	Bladder Catheterization
0	0 (0)	0 (0)	0 (0)	0 (0)
0.2	20 (1)	60 (3)	20 (1)	0 (0)
0.4	60 (3)	80 (4)	40 (2)	0 (0)
0.6	80 (4)	60 (3)	40 (2)	40 (2)

* $P < 0.05$; see text for explanation.

ITMS = intrathecal morphine sulfate.

Isaacson IJ, Weitz FI, Berry AJ, Knos GB, Venner DS: Intrathecal morphine's effect on the postoperative course of patients undergoing abdominal aortic surgery. Anesth Analg 66:S86, 1987.

** Jacobson L, Chabal C: Intrathecal morphine: Efficacy, duration, optimal dose and side effects. Anesth Analg 67:S102, 1988.

In these two studies, the assessment of the respiratory effects of ITMS was limited to RR alone[21] or RR and intermittent blood gas analysis.[22]

The two most significant findings of our study are that ITMS (0.2, 0.4, and 0.6 mg) produces a spectrum of respiratory depression that ranges from mild to severe and that clinical signs or symptoms are unreliable predictors of that respiratory depression, regardless of the degree. Most notably, RR and level of sedation, as well as pupil size and other adverse ITMS effects, did not reliably indicate when mild, moderate, or even severe hypoxemia and ventilatory depression occurred. The significance of these findings is highlighted by the fact that slow RRs and increasing sedation are among the most commonly used clinical indicators employed in monitoring for the presence of potentially troublesome respiratory depression after ITMS. We found that maximum respiratory depression occurred 3.5–7.5 h after ITMS administration. This is consistent with spinal CSF passive flow characteristics that determine the spread of ITMS injected at the lumbar space rostrad to brainstem respiratory centers.[2] Others have documented a similar time to peak ITMS effect, but have noted, as we did, that prolonged and/or delayed respiratory depression, especially with higher ITMS doses, does occur.[2] In our study, for example, subjects receiving 0.6 mg ITMS demonstrated significant depression (<50% of baseline) of the ventilatory response to carbon dioxide up to 19.5 h after ITMS. This, too, is consistent with the fact that disappearance of morphine from the CSF is slow.[3]

The most practical yet effective method for detecting hypoxemia and/or hypoventilation after ITMS is unknown.[3] While slowing of the RR is at times indicative of impending significant opioid-induced respiratory depression, even its hourly monitoring has been deemed "totally unacceptable" after ITMS.[3] Others, too, suggest that RR is not a reliable index of opioid-induced respiratory depression in humans.[23–25] Our findings confirm that RR is neither reliable nor adequate as an indicator of significant respiratory depression after ITMS. While statistically significant ITMS dose effects on sedation and pupil size were detected, the changes in these measures did not clinically precede or coincide with hypoxemia. Others have found opioid-induced pupil diameter changes to be similarly small (in the 0.5–2-mm range) and clinically unhelpful.[26,27] This, combined with the fact that a host of factors can affect sedation and pupil size, renders these unreliable indicators of ITMS-induced respiratory depression. Only pulse oximetry reliably detected inadequate oxygenation in our subjects. While monitoring postoperative patients who have received ITMS with pulse oximetry may be effective, it requires frequent nursing observation, is fraught with false positive signals, and is often impractical. Nevertheless, even if only intermittently applied and/or observed, it may represent the best method available to detect hypoxemia after ITMS, as is the case after general anesthesia.[28,29] Interestingly, at times, the pulse oximeter alarm alone was enough to restore adequate breathing and oxygen saturation in some subjects. One can imagine such a feedback loop in clinical practice as potentially useful, especially if the Sp_{O_2} signal could be stabilized.

Some investigators suggest that prophylactic measures, such as the concomitant systemic administration of opioid antagonists to patients who have received ITMS, may protect them from respiratory depression.[23,30,31] Naloxone infusions are, however, of variable efficacy with regard to relieving respiratory depression and other adverse effects after ITMS.[3] Also, the duration and intensity of analgesia after ITMS can be reduced by naloxone. The actual efficacy and necessary doses of naloxone for preventing troublesome respiratory depression without reducing analgesia after ITMS remains uncertain. Similarly, while naltrexone (3 and 6 mg, orally) reduces ITMS-induced side effects, duration of analgesia is shortened and efficacy and optimal dosage is unknown.[31] The routine application of such prophylactic measures also increases the cost of patient care. Others recommend that ITMS be administered in a hyperbaric solution and that patients retain a head-up position after ITMS injection.[12] While such maneuvers are arguably somewhat effective, they are impractical and unreliable. On the other hand, our results are similar to others'[29] in that oxygen, 2 L/min *via* nasal cannulae, consistently corrected hypoxemia. The inexpensive and practical nature of this prophylactic therapy makes it all the more attractive.

Defining the optimal ITMS dose entails balancing risk and benefit and is complex. Patient age, medical condition, and intensity of pain are likely to be important factors.[3] The subjects in our study were young and healthy and did not have any consistent level of pain. It is possible that the lack of pain predisposed them to greater degrees of respiratory depression than that occurring after ITMS administration in patients with acutely painful conditions. However, a host of factors in the postsurgical patient also impair ventilation and oxygenation. For example, anesthesia reduces lung

volumes and ventilation/perfusion-matching and results in impaired gas exchange. Abdominothoracic surgery and associated pain also can impair breathing through various mechanisms, which include diaphragmatic dysfunction and mechanical splinting. In addition, underlying medical conditions as well as concomitantly administered medications are likely to further impair ventilation and gas exchange. On the whole, it can be argued that our results represent only the "tip of the iceberg" in that our subjects were not affected by one or more of the above-mentioned conditions that are likely to further compromise oxygenation and ventilation in surgical patients. This notion is supported by the findings of Rawal and Wattwil,[32] who demonstrated a greater impairment of ventilation in surgical patients compared to volunteers after similar doses of epidural morphine. On the other hand, we cannot explain how 2.0 and 5.0 mg ITMS were found to produce less depression of the ventilatory response to carbon dioxide in patients after upper abdominal surgery[13] than we found in our present investigation.

The true incidence of hypoxemia or respiratory depression requiring interventions such as naloxone administration after ITMS is unknown but is reported to be as high as 4–7%.[3,15] This is especially true as ITMS dose and patient age increase.[3,15] Others have noted little troublesome respiratory depression with ITMS doses of 0.3–0.5[21] or less[18] and this dosage range may represent the safest compromise when choosing an ITMS dose. In support of this, a ceiling effect for ITMS analgesia may exist in the range of 0.2–0.3 mg.[33] While our data may support this notion (fig. 8, 5–7 h), overall the magnitude and duration of ITMS analgesia was influenced significantly by dose in our study. Animal studies support a ITMS dose or CSF morphine concentration-analgesia relationship.[34,35] In addition, thoracic surgical sites requiring higher neuraxial analgesia[36] or extremely painful conditions may require greater ITMS doses. Nevertheless, our study indicates that ITMS doses of less than 0.6 mg offer some margin of safety compared to doses of 0.6 mg and greater.

The incidence of emesis, one of the more distressing adverse effects of ITMS, was dose-related. While its severity, as gauged by the need for antiemetic medication was independent of dose, the high incidence (80%) of vomiting we observed in subjects receiving 0.6 mg ITMS also favors the application of lower doses. Other adverse ITMS effects are not necessarily dose-related. Pruritus, for example, as others have noted, is not dose-dependent.[3] Pruritus occurred in all our subjects receiving ITMS and was usually the first sign and symptom indicative of central opioid action. Its mechanism and significance remain obscure. Other side effects, notably urinary retention and the need for bladder catheterization, were also not dose-related. While reported frequencies of both these problems vary greatly, they are common, especially after ITMS in young men.[2,3]

We intensively observed our subjects for 24 h. Time-related effects were significant for most variables. The impact of time for example is most apparent at night when systolic blood pressures (fig. 3) and HRs (fig. 2) are lower and Pa_{CO_2}s higher (fig. 5). One can only speculate as to whether ITMS administration late in the day, with peak action occurring late at night, could lead to a higher incidence of adverse respiratory events. Because sleep is known to cause right shifts and decreased slopes in the ventilatory response to carbon dioxide,[37,38] such an increased risk is quite possible. The observed association between nocturnal hypoxemia and postoperative myocardial ischemia in vascular surgery patients supports such a hypothesis.[39] The night-time care and monitoring of patients who have received ITMS may merit at least similar if not increased vigilance as occurs during the day; however, the converse is often the case on many hospital wards.

Other events also can exacerbate ITMS-induced respiratory effects. Postoperative blood loss and hypotension have been noted by some to increase respiratory depression after ITMS.[23,24] Again, night-time, because of its association with lower blood pressures and HRs, may be a period of greater patient vulnerability with regards to postoperative blood loss and worsened respiratory depression. Interestingly, subjects receiving 0.6 mg ITMS in our study did not have the lowest HRs (fig. 2) and had the highest blood pressures (fig. 3) at night. This may have been caused by increased sympathetic nervous system activity associated with hypercarbia, emesis, or other factors.

In summary, ITMS (0.2, 0.4, and 0.6 mg) produces dose-dependent analgesia and respiratory depression. The respiratory depression ranges in magnitude from mild to severe in opioid naive, healthy, human male volunteers. Clinical signs or symptoms, including RR, sedation, and pupil size did not reliably indicate hypoventilation and/or hypoxemia, whereas peripheral pulse oximetry did. The administration of supplemental oxygen, 2 L/min *via* nasal cannulae, was consistently effective in ameliorating hypoxemia associated with ITMS. A high incidence of emesis and urinary retention also occurred after 0.4 and 0.6 mg ITMS. Significant

caution should be exercised with regard to the implications of our findings for patients in the clinical setting. Nevertheless. our study suggests that the optimal ITMS dose in nonopioid-tolerant patients who do not receive intensive care postoperatively may be less than 0.6 mg ITMS. In addition, our study suggests that RR monitoring for detecting significant respiratory depression after ITMS may be inadequate. Patients receiving ITMS would likely experience significant protection against hypoxemia by the application of supplemental oxygen.

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Appendix: SEM for Key Variables

Time	ITMS Dose (mg)	Variable				Time	ITMS Dose (mg)	Variable			
		RR	Pa_{CO_2}	VE/CO_2	PSI			RR	Pa_{CO_2}	VE/CO_2	PSI
Baseline	0.0	01.4	0.88	0.70	01.5	9 h 30 min	0.0	01.1	0.26	0.84	02.6
	0.2	01.0	0.86	0.51	03.0		0.2	03.1	0.84	0.41	02.6
	0.4	01.5	1.18	0.45	02.4		0.4	02.0	1.65	0.41	10.4
	0.6	01.4	1.09	0.71	01.6		0.6	00.8	3.54	0.35	02.5
30 min	0.0	01.0	0.85	0.39	01.7	10 h 30 min	0.0	01.0	0.88	1.16	01.7
	0.2	02.1	1.02	0.34	03.8		0.2	02.1	2.30	0.50	01.9
	0.4	01.0	1.05	0.51	04.0		0.4	01.2	2.19	0.45	07.4
	0.6	01.4	1.17	0.61	00.9		0.6	00.7	2.85	0.34	03.7
1 h 30 min	0.0	01.0	0.97	0.41	01.8	11 h 30 min	0.0	01.7	1.06	0.75	03.0
	0.2	02.1	1.03	0.15	01.1		0.2	01.8	1.57	0.27	01.3
	0.4	01.0	1.44	0.33	02.2		0.4	01.2	2.11	0.39	11.4
	0.6	01.0	1.67	0.43	01.4		0.6	01.6	2.55	0.16	02.1
2 h 30 min	0.0	01.5	0.50	0.82	01.2	13 h 30 min	0.0	01.2	1.59	0.90	02.1
	0.2	01.7	1.44	0.29	04.4		0.2	01.3	1.76	0.29	02.6
	0.4	01.3	1.68	0.12	07.7		0.4	01.2	1.04	0.37	06.3
	0.6	00.8	1.93	0.42	02.5		0.6	01.5	2.92	0.46	03.6
3 h 30 min	0.0	01.4	0.63	0.73	02.1	15 h 30 min	0.0	00.9	1.40	0.68	02.3
	0.2	01.6	2.00	0.33	02.1		0.2	01.5	1.67	0.46	00.8
	0.4	01.8	3.39	0.27	04.4		0.4	01.4	1.16	0.44	03.5
	0.6	01.3	2.41	0.26	04.0		0.6	01.8	2.88	0.41	03.5
4 h 30 min	0.0	01.2	0.71	1.15	01.7	17 h 30 min	0.0	01.5	1.46	0.64	03.4
	0.2	02.4	1.51	0.64	04.6		0.2	00.8	0.78	0.44	02.0
	0.4	01.4	2.74	0.51	05.8		0.4	01.0	1.59	0.27	04.7
	0.6	01.2	1.70	0.16	01.9		0.6	01.4	0.99	0.38	04.1
5 h 30 min	0.0	01.3	0.96	1.04	02.1	19 h 30 min	0.0	01.3	0.58	0.88	02.7
	0.2	02.2	2.58	0.51	01.5		0.2	01.0	1.03	0.35	01.4
	0.4	01.6	2.34	0.15	04.7		0.4	02.1	1.87	0.22	02.7
	0.6	00.9	1.76	0.36	05.1		0.6	01.5	1.91	0.25	03.2
6 h 30 min	0.0	01.4	0.73	1.20	00.8	21 h 30 min	0.0	01.9	1.18	0.82	01.4
	0.2	02.4	1.59	0.39	03.5		0.2	01.2	1.55	0.54	00.0
	0.4	02.0	2.35	0.40	07.3		0.4	01.5	1.53	0.30	02.6
	0.6	00.8	2.18	0.22	03.4		0.6	00.6	1.38	0.43	01.2
7 h 30 min	0.0	01.4	0.89	0.74	01.4	23 h 30 min	0.0	01.3	1.59	0.59	01.2
	0.2	02.1	1.55	0.45	04.0		0.2	01.1	1.06	0.56	04.8
	0.4	02.4	1.98	0.29	09.9		0.4	00.5	1.22	0.47	02.7
	0.6	00.5	2.25	0.28	03.7		0.6	00.9	1.04	0.53	04.1
8 h 30 min	0.0	01.5	0.91	0.82	02.3						
	0.2	02.2	2.41	0.52	03.1						
	0.4	02.2	2.90	0.32	07.2						
	0.6	00.7	1.69	0.21	02.2						