The Effect of Intrathecal Morphine on Somatosensory Evoked Potentials in Awake Humans

Armin Schubert, M.D.,* Michael G. Licina, M.D.,* Paul J. Lineberry, M.D.,† Mark A. Deers, M.A.‡

Although the effect of systemic opioids on somatosensory evoked potentials has been well described, little is known about the interaction between intrathecially administered opioid analgesics and somatosensory evoked potentials. Accordingly, the influence of intrathecally administered morphine on posterior tibial nerve somatosensory cortical evoked potentials (PTSCPEs) was investigated in 22 unpremedicated, awake, neurologically normal patients scheduled to undergo elective abdominal or pelvic procedures. Patients were randomly assigned to receive either preservative-free intrathecal morphine sulfate (ITMS) or placebo. After baseline PTSCPE, heart rate and, mean blood pressure were recorded, ITMS (15 µg · kg⁻¹) was injected into standard dural puncture with the patient in the lateral position. PTSCPEs, heart rate, and mean blood pressure were recorded again at 5, 10, 20, 30, 60, 90, and 120 min. Control patients were treated identically (including position, sterile preparation, and subcutaneous tissue infiltration with local anesthetic), except for lumbar puncture, and were unaware of their randomization. Before administration of ITMS, PTSCPE P1, N2, P2, N2, and P2 latencies were 39.4 ± 3.2, 47.6 ± 3.9, 59.2 ± 3.2, 70.4 ± 3.7, and 84.6 ± 5.5 ms, (mean ± standard deviation), respectively. The corresponding P1-N2, N2-P2, and P2-N2 amplitudes were 2.4 ± 1.1, 2.4 ± 1.1, and 2.3 ± 0.9 µV, respectively. There were no significant changes over time between the control and ITMS groups. PTSCPEs resulting from left-sided stimulation were not different from those elicited by right-sided stimulation. All ITMS patients had intense postoperative analgesia for at least 24 h. It is concluded that ITMS does not affect PTSCPE waveforms in the 35–90-ms latency range during the awake state. This suggests that opioid-activated spinal pathways do not intervene with transmission of afferent impulses resulting from electrical stimulation of a peripheral somatic nerve.

(Key words: Analgesics, intrathecal: morphine. Monitoring: evoked potentials; somatosensory.)

INTRATHECALLY ADMINISTERED MORPHINE (ITMS) has been used extensively in the control of chronic malignant and acute postoperative pain. It is frequently administered before and during aortic,¹ cardiac,²,³ and spine surgery.⁴ During these procedures, the central nervous system can be at risk for ischemic injury. In many health care centers, therefore, somatosensory evoked potentials are monitored to assess the integrity of critical neural pathways. Knowledge of the effect of ITMS on somatosensory evoked potentials can be expected to facilitate their interpretation.

While spinaly applied opioids primarily suppress noxious C- and Aδ-fiber evoked electrical activity,⁵ even activity in Aβ fibers, which conduct evoked potentials and are believed to resist modulation by opioids,⁶ is depressed by meperidine.⁷ This, with the knowledge that systemic opioids can reduce somatosensory evoked potential amplitude, prompted our concern that intrathecal morphine also might influence the appearance of posterior tibial nerve somatosensory cortical evoked potentials (PTSCPEs) and affect their interpretation. The extent of this interaction would be of interest both during perioperative neurologic monitoring and when evoked potentials are used for assessment of analgesic potency⁸,⁹ or tolerance.¹⁰ The present study was carried out to evaluate the influence of intrathecialy administered morphine on PTSCPEs in awake humans.

Materials and Methods

Institutional approval was granted and each patient gave written informed consent. Twenty-two neurologically normal adult patients scheduled to undergo elective pelvic and abdominal procedures were randomly assigned to receive either intrathecal morphine sulfate (ITMS) or placebo. No preanesthetic medication was given. Patients were brought to the preoperative area approximately 2.5 h before the start of the procedure, when baseline lower-extremity PTSCPEs were recorded. Immediately thereafter, ITMS patients were turned to the right lateral decubitus and were given undiluted preservative-free ITMS (15 µg · kg⁻¹). After skin infiltration with 1% lidocaine (≤ 3 ml), dural puncture was carried out under sterile conditions, using a 25-G spinal needle at the L₄–L₅ interspace. Subarachnoid puncture was confirmed by aspiration of cerebrospinal fluid before and after injection. The patient was turned supine, and PTSCPEs were again recorded at 5, 10, 20, 30, 60, 90, and 120 min. All recordings were made before the start of general anesthesia. Control patients were treated identically (including position, sterile preparation, and subcutaneous tissue infiltration with local anesthetic), except for lumbar puncture.

Right and left lower-extremity PTSCPEs were elicited sequentially by stimulation of the posterior tibial nerve using a Pathfinder II Electrodiagnostic Monitoring System.
TABLE 1. Demographic and Baseline Hemodynamic Variables

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>ITMS</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>32 ± 9</td>
<td>33 ± 8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71 ± 10</td>
<td>71 ± 14</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>167 ± 8</td>
<td>174 ± 12</td>
</tr>
<tr>
<td>HR (beats per min)</td>
<td>77 ± 8</td>
<td>72 ± 10</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>87 ± 11</td>
<td>84 ± 7</td>
</tr>
</tbody>
</table>

Data are means ± SD. HR = heart rate; MBP = mean blood pressure.

(Nicolet Biomedical, Madison, WI). Recordings were obtained from gold-cup surface electrodes positioned at C3, (active), C4 (reference), and the mastoid process (ground), according to the International 10-20 System. Electrode impedance was restricted to < 3 kOhms. A constant-current, 200-μs stimulus was delivered to adhesive electrodes overlying the posterior tibial nerve at each ankle. The stimulus was applied at an intensity of motor threshold plus 2 mA and was repeated 400 times at 3.1 Hz. The signal was recorded over a 140-ms time base using bandpass filters of 30 and 500 Hz and was amplified 120,000 times (corresponding to a Pathfinder II sensitivity setting of 50). The waveforms of interest consisted of a positive deflection at approximately 37 ms (P1), followed by a negativity at approximately 45 ms (N1), and successive positive, negative, and positive deflections at 56, 68, and 82 ms, respectively. The waveforms were stored on magnetic disc. An experienced, blinded observer, having identified waveform peaks with electronic cursors, later computed latency and trough-to-peak amplitude. With each PTSCEP recording, mean systemic blood pressure, heart rate, and cutaneous level of anesthesia to pinwheel were measured. The stimulated extremities were kept warm by wrapping them in blankets.

Baseline vital signs and demographic data were compared between the two groups using unpaired t tests. Since there were differences in baseline PTSCEP measurements in the control and ITMS groups, the absolute and percent differences between baseline and posttreatment PTSCEP parameters were computed and compared using a three-way repeated-measures analysis of variance to determine if there were any significant differences 1) between right- and left-sided stimulation, 2) over time, and 3) between the control and ITMS groups. The actual PTSCEP amplitudes and latencies also were separately analyzed by repeated-measures analysis of variance to detect any changes over time when compared to baseline. Where the analysis of variance detected significance, Tukey's procedure for multiple comparisons was used to identify differences between pairs. Statistical significance was assumed at the P ≤ 0.05 level.

Results

Both groups were equivalent with respect to demographic parameters and baseline mean systemic blood pressure and heart rate (table 1). Mean systemic blood pressure and heart rate remained unchanged with time. Five of 11 ITMS patients developed an identifiable area of cutaneous hypesthesia within 2 h of drug administration; onset times ranged from 30 to 120 min. In all cases, PTSCEPs were recorded without difficulty throughout the study period (fig. 1). Pretreatment PTSCEP latencies and amplitude appear in table 2. Absolute latencies and amplitudes remained unchanged after treatment in both the ITMS and control groups. The behavior of early PTSCEP latency (P1) and amplitude (P1–N1) after ITMS is illustrated in table 3. There were no significant changes in amplitude or latency after ITMS. With one minor exception, the absolute and percent differences of post-treatment latencies and amplitudes compared to pretreatment baseline were similar between groups and be-

<table>
<thead>
<tr>
<th>Latency</th>
<th>Control R</th>
<th>Control L</th>
<th>ITMS R</th>
<th>ITMS L</th>
</tr>
</thead>
<tbody>
<tr>
<td>P&lt;sub&gt;1&lt;/sub&gt;</td>
<td>37.2 ± 4.2</td>
<td>37.2 ± 3.7</td>
<td>39.4 ± 3.3</td>
<td>39.0 ± 3.1</td>
</tr>
<tr>
<td>N&lt;sub&gt;1&lt;/sub&gt;</td>
<td>45.1 ± 5.0</td>
<td>44.1 ± 2.6</td>
<td>47.6 ± 3.9</td>
<td>45.9 ± 3.4</td>
</tr>
<tr>
<td>P&lt;sub&gt;2&lt;/sub&gt;</td>
<td>56.2 ± 5.4</td>
<td>55.9 ± 2.9</td>
<td>59.2 ± 3.2</td>
<td>56.9 ± 3.9</td>
</tr>
<tr>
<td>N&lt;sub&gt;2&lt;/sub&gt;</td>
<td>68.4 ± 2.4</td>
<td>68.7 ± 1.7</td>
<td>70.4 ± 3.7</td>
<td>70.0 ± 3.8</td>
</tr>
<tr>
<td>P&lt;sub&gt;3&lt;/sub&gt;</td>
<td>81.9 ± 5.4</td>
<td>82.7 ± 4.5</td>
<td>84.6 ± 5.5</td>
<td>84.7 ± 5.6</td>
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Amplitude

| P<sub>1</sub>–N<sub>1</sub> | 2.2 ± 0.8 | 2.1 ± 0.9 | 2.4 ± 1.1 | 1.7 ± 1.0 |
| N<sub>1</sub>–P<sub>2</sub> | 2.6 ± 1.1 | 2.4 ± 1.0 | 2.4 ± 1.1 | 2.0 ± 1.1 |
| P<sub>2</sub>–N<sub>2</sub> | 2.8 ± 1.2 | 2.7 ± 1.2 | 2.3 ± 0.9 | 1.9 ± 0.7 |

Values are means ± SD.

ITMS = intrathecal morphine sulfate; R = right; L = left.
TABLE 3. Early Cortical Latency and Amplitude after Intrathecal Morphine Sulfate

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>5</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>( P_1 ) latency (ms)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>39.4 ± 3.3</td>
<td>41.1 ± 3.0</td>
<td>40.3 ± 2.7</td>
<td>40.6 ± 3.4</td>
<td>39.5 ± 4.2</td>
<td>39.8 ± 3.9</td>
<td>40.8 ± 4.3</td>
<td>39.6 ± 4.3</td>
</tr>
<tr>
<td>Left</td>
<td>39.0 ± 3.2</td>
<td>39.0 ± 3.2</td>
<td>39.5 ± 3.3</td>
<td>39.7 ± 3.6</td>
<td>39.2 ± 3.3</td>
<td>38.4 ± 4.2</td>
<td>39.4 ± 3.5</td>
<td>39.7 ± 3.3</td>
</tr>
<tr>
<td>( P_1-N_1 ) amplitude (μV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>2.4 ± 1.1</td>
<td>2.0 ± 0.9</td>
<td>1.9 ± 0.8</td>
<td>1.9 ± 0.6</td>
<td>2.1 ± 1.2</td>
<td>1.5 ± 0.7</td>
<td>1.5 ± 0.7</td>
<td>1.9 ± 1.1</td>
</tr>
<tr>
<td>Left</td>
<td>1.7 ± 1.0</td>
<td>2.3 ± 1.2</td>
<td>2.4 ± 1.1</td>
<td>2.4 ± 0.8</td>
<td>2.4 ± 1.0</td>
<td>2.3 ± 1.0</td>
<td>2.5 ± 1.0</td>
<td>2.1 ± 0.9</td>
</tr>
</tbody>
</table>

Data are means ± SD.

tween sides of stimulation. Only the differences between groups with respect to percent change from the \( N_1-P_2 \) baseline amplitude achieved significance \( (P = 0.03) \).

Postoperatively, all ITMS patients had pain relief without additional analgesics for at least 24 h. However, 10 of 11 ITMS patients required a naloxone infusion for side effects related to ITMS.

Because of the general lack of differences observed, the statistical power of our analysis was evaluated, assuming that a latency change of 10% and an amplitude change of 50% would be clinically important.\(^\text{12}\) For the most part, statistical power was high. For example, for \( N_1 \) latency changes over time, power ranged from 78 to 99%.

**Discussion**

Our results indicate that the lower-extremity cortical somatosensory evoked potential waveform remains unaffected despite the administration of a relatively high dose of ITMS. This implies that opioid-related neural effects at the spinal cord level do not affect neural transmission of afferent impulses resulting from electrical stimulation of a somatic nerve. The effects are unlike the somewhat depressant effect of systemic opioids,\(^\text{13-15}\)§ which presumably act at a supraspinal level. ITMS exerted no differential effects on the right as compared to the left stimulated PTSCEP, arguing against position-related or other lateralizing effects (because all of our patients received ITMS in the right lateral decubitus).

Presumably, ITMS does not have an effect on PTSCEPs because morphine does not act upon the spinal cord pathways responsible for conducting somatosensory evoked potentials.


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**Fig. 1.** The lack of effect of intrathecal morphine sulfate on right (A) and left (B) stimulated posterior tibial nerve somatosensory cortical evoked potentials. PRE = pre-ITMS baseline.
potentials. They are believed to travel primarily in the dorsal column pathways, but evidence for alternate conduction also has been reported. Although subarachnoid opioids suppress nociceptive spinal reflexes, electrically stimulated cutaneous evoked potentials are carried by \( A \beta \) fibers, which do not carry major nociceptive inputs. Furthermore, morphine selectively suppresses spontaneous firing in neurons responding to noxious stimuli, while leaving neurons that respond to proprioceptive input relatively unaffected. The dorsal column pathway does not seem to be associated with opiate receptors. This explains the lack of effect of spinally administered morphine on PTSCPEs. Also, early components of the somatosensory evoked response are conducted \( \text{via} \) large \( A \) fibers, which are not readily blocked by peridural opioids. In contrast, \( C \) fibers apparently conduct later (> 500 ms) components of the evoked response. It is conceivable that we would have observed an effect on these later components had we monitored a longer time base after stimulus delivery. However, the longer-latency components are generally of little value in perioperative monitoring for neurologic integrity because they are exquisitely sensitive to anesthetic and other environmental influences. Of note is the observation by Paulus et al. that larger doses of intrathecal morphine may result in depression of consciousness 4–10 h after administration. They postulated a cerebral effect related to slow cranial diffusion of morphine. Hence, it is conceivable that ITMS may alter PTSCPEs by virtue of its delayed, supraspinal action. However, this probably would be seen only with even higher doses than those used in the present investigation.

Nevertheless, our negative results confirm those of a recent preliminary report on ITMS administered intraperitoneally. Furthermore, they agree with previous work investigating the effect of intrathecal fentanyl and epidural morphine on cortical somatosensory evoked potentials. Lack of statistical power does not explain why we did not observe significant PTSCPE changes after ITMS. The ability to aspirate CSF before and after injection of ITMS, together with the unequivocal clinical analgesic effect observed postoperatively, indicates that all our ITMS patients were subject to the action of ITMS.

Our observations have limited practical implications in the anesthetic management of patients undergoing major vascular and spine surgery, when ITMS is a rational choice for postoperative analgesia, but the PTSCPE must also be monitored. The present data indicate that, at least during the first 2 h, ITMS does not materially affect PTSCPEs. Our study does not address the question of delayed evoked potential changes that may be associated with the onset of ITMS's supraspinal action. The clinical significance of such changes appears doubtful, because a lag time of 4–6 h would be expected, and in most cases the recording of PTSCPEs should occur before this time.

We conclude that ITMS does not interfere with the recording of unilaterally stimulated PTSCPEs in awake patients and does not affect the latency and amplitude of cortical waveforms in the 35–90-ms latency range for up to 2 h after administration.

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References