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Lumbar Epidural Morphine in Humans and Supraspinal Analgesia to Experimental Heat Pain

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Background: Epidural administration of morphine is a common analgesic technique to manage pain. Morphine spreads from the epidural space to the cerebrospinal fluid and then rostrally, causing side effects mediated by the brain stem. However, data on the rostral spread of morphine-mediated analgesia are sparse. This study examined the rostral spread of analgesic effects on heat and electrical pain after epidural administration of morphine.

Methods: In a randomized, double-blinded, placebo-controlled, crossover study, 5 mg morphine or saline placebo were injected into the lumbar epidural space in nine healthy volunteers. Correct needle placement was confirmed with fluoroscopy. Analgesia to experimental nociceptive heat and electrical stimuli was measured at lumbar (L4), thoracic (T10), cervical (C2), and trigeminal (V2) levels before and 2, 5, 10, and 24 h after epidural injection. Plasma samples for assaying morphine concentrations were drawn before and after each analgesic evaluation.

Results: Epidural morphine significantly attenuated experimental heat pain at all dermatomes compared with saline placebo. Analgesic effects were significant at L4 after 2, 5, and 10 h, at T10 after 5, 10, and 24 h, and at V2 after 10 h. Electrical pain was attenuated at the lumbar and thoracic but not at the cervical dermatome. Analgesic effects were significant at L4

after 2, 5, and 10 h and at T10 after 5 and 10 h. Morphine plasma concentrations were below the detection limit (1 ng/ml) in eight of the nine subjects 10 h after epidural injection.

Conclusions: Lumbar epidural injection of morphine attenuated cutaneous heat pain up to the trigeminal dermatome during a 24-h observation period. In a clinical context, this implies that some types of pain may be attenuated up to the supraspinal level after lumbar epidural administration of morphine. (Key words: Electricity; opioid; pharmacodynamics; spinal cord; temperature.)

OVER the last two decades, epidural and intrathecal administration of opioids has become a standard for treating acute and chronic pain.¹⁻³ Opioids exert a prominent analgesic action at the level of the spinal dorsal horn.⁴ Opioids also spread rostrally in the cerebrospinal fluid and may act at the brain stem.⁵⁻⁷ Common side effects associated with the use of spinal opioids and that involve brain-stem mechanisms are facial pruritus, nausea, and sedation.⁸

Among opioids, morphine most prominently spreads rostrally because of its low lipid solubility.⁵⁻⁷ However, only few studies have examined the rostral spread of analgesic effects after epidural administration of morphine.⁹⁻¹² Interpretation of the results of some of these studies is limited because it is unclear whether the observed supraspinal action is the result of an intrathecal rostral spread or a significant initial uptake of morphine into the systemic circulation with subsequent distribution to the brain.^{10,11,13-15} However, two unblinded studies demonstrated that analgesia to pin-prick pain spread to thoracic and supraspinal levels after lumbar epidural administration of 4 and 10 mg morphine, respectively.^{9,12} These studies had sufficiently long observation periods (7 and 22 h) to make the intrathecal rostral spread the likely underlying mechanism.

The goal of this study was to determine the spread of analgesia to experimental heat and electrical pain after epidural administration of 5 mg morphine and saline placebo, respectively.

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Methods

Subjects

Nine healthy volunteers gave written informed consent for the study, which was approved by the Institutional Review Board of Stanford University. All subjects had a negative physical examination, an unremarkable medical history, and did not take any medications.

Study Design

This study used a randomized, double-blinded, placebo-controlled, crossover design. Either morphine or normal saline was injected into the epidural space during two sessions at least 6 days apart. Study sessions started at 7 AM in an isolated and quiet room at an ambient temperature that was comfortable to the subjects. An intravenous catheter was placed in one arm for blood drawings. Subjects remained semirecumbent throughout the study.

Drug Administration

An 18-gauge Touhy needle was inserted midline *via* the L2/L3 or L3/L4 interspace. Subjects were in the right lateral position. The epidural space was identified by loss of resistance to air. Either 5 mg preservative-free morphine (Abbott Laboratories, North Chicago, IL) diluted in 10 ml normal saline or 10 ml plain normal saline was injected over a period of 60 s *via* syringe pump (Harvard Pump 22; Harvard Apparatus Inc., South Natick, MA). The investigator who prepared and administered the drug did not take any further part in the study. Immediately after drug administration, an 18-gauge epidural catheter was inserted through the needle up to 5 cm into the epidural space. Five hours after epidural drug administration, 10 ml radio-opaque dye (Omnipaque; Nycomed Inc., Princeton, NJ) was injected through the epidural catheter. Fluoroscopy confirmed the correct placement of the epidural catheter.

Experimental Pain Tests

Nociceptive heat and electrical stimuli were used to test for analgesic effects after administration of epidural morphine or saline placebo. The lowest temperature evoking pain (pain threshold) and the highest temperature tolerated (pain tolerance) were determined using a small metal plate in contact with skin. The lowest current evoking pain and the highest current tolerated were determined using a skin-surface electrode. Recordings were made at baseline and 2, 5, 10, and 24 h after drug administration. During each analgesic measurement pe-

riod, three different dermatomes were evaluated in random sequence. The lumbar and thoracic dermatomes tested for nociceptive heat and electrical stimuli were identical. However, the most cranial dermatomes tested for nociceptive heat and electrical stimuli were different. The cheek was used to test as far rostral as possible for nociceptive heat stimuli. This or a nearby facial location could not be used for nociceptive electrical stimuli because such stimulation not only evoked pain but also muscular twitching proportional in strength to underlying stimulus intensity (not observed for lumbar and thoracic location). The perceived magnitude of a muscular twitch provides a clue about the intensity of administered nociceptive stimulus and in this way may bias and invalidate how subjects rate the magnitude of evoked pain. Therefore, the pinna of the ear was used as the most rostral dermatome feasible for electrical stimulation. To familiarize subjects with the test procedure, they all underwent two sessions of experimental pain testing a week before the study.

Heat Pain Testing

A thermal sensory analyzer (TSA 2001; Medoc Advanced Medical Systems, Minneapolis, MN) was used to administer the nociceptive heat stimuli. An investigator brought a hand-held 16 × 16-mm thermode in full contact with the subject's skin. After equilibration between skin and the thermode at 35°C, the temperature of the thermode increased 1°C/s. The thermode could be heated to a maximum temperature of 53°C. First, subjects pushed the button of a hand-held device as soon as they felt pain, thereby triggering the recording of the temperature that caused pain as well as the immediate cooling of the probe. This procedure was performed three times per dermatome at sites at least 2.5 cm apart, and the average of the minimal temperature evoking pain was recorded. Using the same algorithm, subjects pushed the button of the hand-held device as soon as they were unable to tolerate the evoked pain. The average of the maximum-tolerated temperature was recorded. The interstimulus interval was 30 s. If a subject was able to tolerate the maximum output temperature of the device (53°C), this was recorded as the maximum-tolerated temperature (24 of 810 recordings). The dermatomes evaluated for nociceptive heat stimuli were L4 (lateral to the tibia), T10 (lateral to the umbilicus), and V2 (cheek). At the beginning of each test cycle, standardized sentences were read to the subjects emphasizing the algorithm of the procedure.

Electrical Pain Testing

A constant-current device (Neurometer; Neurotron Inc., Baltimore, MD) with a maximum output of 20 mA and delivering 5-Hz sine wave pulses was used to administer nociceptive electrical stimuli. A ring electrode (outer aluminum electrode 16 mm wide and concentric to a central gold electrode 5 mm in diameter; distance between adjacent margins was 14 mm) was attached to the surface of the skin. The electrical pain threshold was determined by delivering at first a non-noxious stimulus randomly ranging between 80 and 160 μ A. The second stimulus was 50% higher than the first one. The magnitude of subsequent stimuli was determined by a subject's response to the two preceding stimuli. If a subject's response to two preceding stimuli was "no pain—no pain" or "pain—pain" the next stimulus was equal to the magnitude of the last delivered stimulus plus or minus 130% of the difference between the last and the second last stimulus, respectively. If a subject's response to two preceding stimuli was "no pain—pain" or "pain—no pain," the next stimulus was equal to the magnitude of the second last stimulus plus 75% or 25% of the difference between the last and the second last stimulus, respectively. The purpose of outlined algorithm was to increase or decrease the magnitude of delivered stimuli quickly as long as a subject gave a uniform response, *i.e.*, "no pain" or "pain." However, whenever a subject changed the response from "no pain" to "pain" or from "pain" to "no pain," the outlined algorithm allowed exploring the magnitude of stimuli evoking a change in response at a higher resolution. Once the value of the highest current evoking no pain and the lowest current evoking pain deviated by no more than 10% from each other, their average was recorded as the pain threshold. The electrical pain tolerance was determined by delivering at first a stimulus randomly ranging between 160 and 240 μ A. The magnitude of each subsequent stimulus was increased by 15%. The stimulus series stopped as soon as a subject indicated that the next higher stimulus would induce intolerable pain. None of the subjects reached the maximum output of the constant current device. This procedure was performed twice per dermatome, and the average of the maximum-tolerated current was recorded. The stimulus duration was 3 s, and the inter-stimulus interval was 15 s. The dermatomes evaluated were L4 (lateral to the tibia), T10 (paraspinal), and C2 (pinna of the ear with a modified ring electrode). At the beginning of each test cycle, standardized sentences were read to the subjects, emphasizing the algorithm of the procedure.

Plasma Morphine Concentration

Five milliliters of venous blood was collected into a heparinized tube to determine the plasma morphine concentration before and 2, 3, 5, 6, 10, 11, 24, and 25 h after epidural drug injection. Samples were immediately put on ice, centrifuged within 2 h, and stored at -20°C .

The assay for morphine was conducted at the Bioanalytical Laboratory of the Pain Research Program at Fred Hutchinson Cancer Research Center, Seattle, Washington. Morphine plasma concentrations were determined with an HP 5890II gas chromatograph and HP 5989A mass spectrometer (Agilent Technologies, Palo Alto, CA). Nalorphine as internal standard (20 ng), boric acid/sodium borate buffer (1 ml; pH = 8.9), and a chloroform isopropyl alcohol mixture (4 ml; ratio 95:5) were added to each sample (0.5 ml). Samples were shaken (150 rpm) for 15 min and centrifuged for 10 min (3,000 rpm). The aqueous layer was removed by suction. The organic layer was evaporated to dryness under a stream of nitrogen (65°C). After cooling to room temperature, 50 μ l pentafluoropropionic anhydride was added and the tubes were immediately capped and heated to 65°C for 45 min. Pentafluoropropionic anhydride was evaporated under a stream of nitrogen at room temperature. The residue was reconstituted in ethyl acetate (100 μ l) and injected on the gas chromatograph/mass spectrometer (1–2 μ l). Standard curves were prepared daily for concentrations between 2 and 400 ng/ml. Spiked control samples had concentrations of 30 ng/ml and 150 ng/ml, respectively. The within-day coefficients of variation were 9.2 and 10.9%, and the between-day coefficients of variation were 10.6 and 12.6%, respectively. The limit of quantification was 1 ng/ml.

Vital Signs and Adverse Events

Blood pressure, heart rate, respiratory rate, and hemoglobin oxygen saturation were assessed noninvasively at baseline, every 15 min during the first 2 h after drug administration, and then hourly up to 24 h. Adverse events were recorded.

Data Analysis

To determine drug effect on the minimum thermode temperature evoking pain (heat pain threshold) and the maximum-tolerated thermode temperature (heat pain tolerance), individual readings before epidural drug administration were subtracted from readings obtained 2, 5, 10, and 24 h after drug administration. The difference from baseline was used because temperature is measured on an interval scale that precludes expressing a change in temperature as a percentage. The area under the curve (AUC;

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Table 1. Heat Pain Threshold and Heat Pain Tolerance at Three Dermatomes before and after Lumbar Epidural Administration of 5-mg Morphine and Saline Placebo

	Pain Threshold (°C)		Pain Tolerance (°C)	
	Morphine	Saline Placebo	Morphine	Saline Placebo
Lumbar 4*				
0 h	45.3 ± 2.0	46.3 ± 2.2	48.9 ± 1.8	49.5 ± 1.3
2 h	47.0 ± 1.9 [‡]	46.2 ± 2.3	49.8 ± 1.3 [‡]	49.0 ± 1.6
5 h	48.0 ± 2.1 [‡]	46.3 ± 1.7	49.9 ± 1.2 [‡]	48.9 ± 1.5
10 h	47.6 ± 2.7 [‡]	45.9 ± 1.8	49.9 ± 1.8 [‡]	48.8 ± 2.0
24 h	46.8 ± 1.8	46.3 ± 1.7	49.5 ± 1.5	49.3 ± 1.6
Thoracic 10*				
0 h	43.1 ± 1.5	44.3 ± 2.1	47.5 ± 1.7	47.8 ± 1.8
2 h	44.9 ± 1.8*	44.7 ± 2.3	48.1 ± 1.6	47.6 ± 1.9
5 h	45.9 ± 2.2*	44.7 ± 1.8	48.5 ± 1.7 [‡]	47.4 ± 1.7
10 h	45.8 ± 1.8*	44.4 ± 2.0	48.5 ± 2.0 [‡]	47.1 ± 1.6
24 h	45.7 ± 1.4	44.7 ± 2.2	48.1 ± 1.7 [‡]	47.4 ± 1.7
Trigeminal 2 [†]				
0 h	44.5 ± 2.0	44.7 ± 3.3	48.2 ± 1.7	48.5 ± 2.4
2 h	45.3 ± 2.7	44.9 ± 3.2	48.8 ± 1.2	48.1 ± 2.7
5 h	46.5 ± 1.8	45.4 ± 2.8	48.9 ± 1.9	48.3 ± 2.3
10 h	46.6 ± 2.3	45.4 ± 3.4	49.1 ± 2.1 [‡]	48.4 ± 2.4
24 h	46.3 ± 2.3	45.3 ± 2.7	49.1 ± 1.9	48.7 ± 2.4

Values are mean ± SD.

$P < 0.05$ with Bonferroni correction.

* Epidural injection of morphine and saline placebo resulted in a significantly different area under the curve (AUC) describing the difference of the heat pain threshold and the heat pain tolerance from baseline *versus* time, respectively.

[†] Epidural injection of morphine and saline placebo resulted in a significantly different AUC describing the difference of the heat pain tolerance from baseline *versus* time. The AUC describing the difference of the heat pain threshold from baseline *versus* time was not significantly different but tended to be larger after epidural injection of morphine.

[‡] Times when a significantly different heat pain threshold and/or heat pain tolerance was measured (difference from baseline) between epidural injection of morphine and saline placebo.

describing differences of the thermode temperature *versus* time was calculated for each subject. Six individual AUCs describing the effect of epidural morphine or saline on the pain threshold and the pain tolerance at L4, T10, and V2 were derived, respectively. The AUC was calculated by the trapezoidal rule using linear interpolation.

To determine drug effect on the minimum current evoking pain (electrical pain threshold) and the maximum-tolerated current (electrical pain tolerance), individual readings obtained at 2, 5, 10 and 24 h after epidural drug administration were expressed as the percentage change from the reading recorded before epidural drug injection. The AUC describing the percentage change of administered current *versus* time was calculated as outlined previously.

The statistical analysis aimed to address two questions. First, at which dermatomes does morphine produce significant analgesia when compared with saline placebo? Second, at what times after epidural injection was this effect significant compared with saline

placebo? To address the first question, individual AUCs depicting the pain threshold or the pain tolerance *versus* time after epidural morphine and saline placebo injection were compared (paired *t* test or Wilcoxon signed rank test). Because such comparison was made at three dermatomes, a *P* value of 0.017 (Bonferroni's correction) was considered statistically significant. If epidural morphine produced significant analgesia at a particular dermatome, morphine and saline placebo treatments were compared at 2, 5, 10, and 24 h after epidural injection. A *P* value of 0.0125 (Bonferroni's correction) was considered statistically significant because four comparisons were made. The paired test procedure (paired *t* test or Wilcoxon signed rank test) was preferred to a three-factorial analysis of variance because not all of the pain tolerance and pain threshold data were normally distributed, nor was the sphericity assumption implicit to the analysis of variance supported. All data are presented as mean and SD unless otherwise stated.

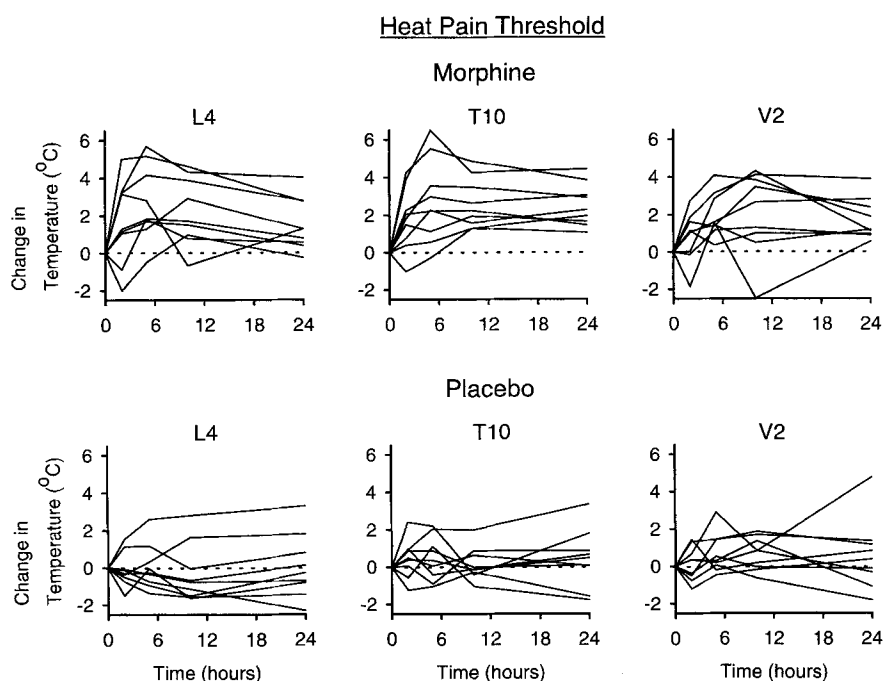


Fig. 1. Hairball plots depict individual changes of the heat pain threshold *versus* time in nine subjects. The three upper plots display the difference from baseline at the lumbar (L4), thoracic (T10), and trigeminal (V2) dermatome after epidural administration of morphine. The three lower plots display the same measurements after epidural injection of saline placebo.

Results

Subjects

All of the five male and four female subjects (age 26 ± 5 yr, weight 55 to 96 kg) completed the study.

Drug Administration

The epidural space was identified in all subjects on the first attempt. After placement of the epidural needle, all attempts to aspirate fluid were negative. Correct placement of the catheter inserted through the epidural needle after drug administration was confirmed by fluoroscopy of the lumbar spine. The radio-opaque dye injected showed the typical column-like spread within the epidural space reaching a rostral level of L1 to T10 after the 60-s injection period.

Thermal Experimental Pain Testing

Table 1 lists the raw values of the heat pain threshold and the heat pain tolerance obtained at L4, T10, and V2 before and after epidural administration of morphine and saline placebo, respectively. In contrast, figures 1 and 2 depict individual changes of the heat pain threshold and the heat pain tolerance from baseline at L4, T10, and V2 after morphine (top graphs) and saline placebo (bottom graphs), respectively. Figure 3 summarizes the individual data presented in figures 1 and 2, depicting the average change of

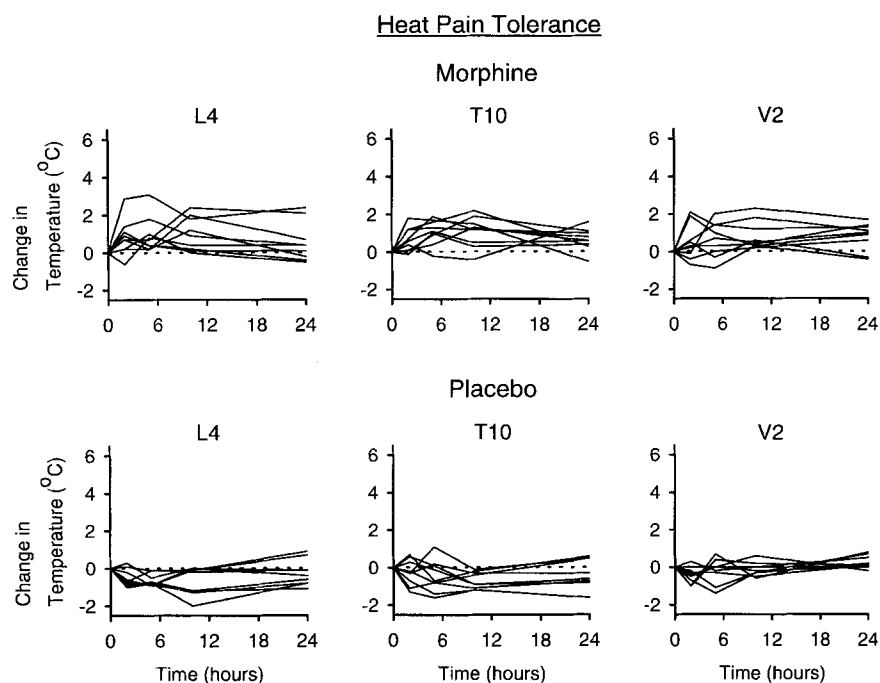
the heat pain threshold (top graphs) and the heat pain tolerance (bottom graphs) from baseline.

The heat pain threshold increased at all dermatomes after epidural morphine but did not change or increased just slightly after epidural saline injection. The heat pain threshold peaked between 5 and 10 h and remained elevated during the 24-h observation period. Changes were more pronounced at L4 and T10 than at V2. The AUC describing the difference of the heat pain threshold from baseline *versus* time was significantly different between epidural morphine and saline injections at L4 and T10 ($P < 0.017$). The AUC describing the difference of the heat pain threshold from baseline *versus* time at V2 was not significantly different but tended to be larger after epidural injection of morphine ($P = 0.12$). Comparing epidural morphine with epidural saline injections, the heat pain threshold was significantly increased at L4 and T10 after 2, 5, and 10 h and after 5, 10, and 24 h, respectively.

The heat pain tolerance increased at all dermatomes after epidural morphine but did not change or decreased after epidural saline injection. The heat pain tolerance peaked between 5 and 10 h and remained elevated during the 24-h observation period. Changes were more pronounced at L4 and T10 than at V2. The AUC describing the difference of the heat pain tolerance from baseline *versus* time was significantly different between epidural morphine and saline injections at all dermatomes

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Fig. 2. Hairball plots depict individual changes of the heat pain tolerance *versus* time in nine subjects. The three upper plots display the difference from baseline at the lumbar (L4), thoracic (T10), and trigeminal (V2) dermatome after epidural administration of morphine. The three lower plots display the same measurements after epidural injection of saline placebo.



tested ($P < 0.017$). Comparing epidural morphine with epidural saline injections, the heat pain tolerance was significantly increased at L4 after 2, 5, and 10 h; at T10 after 5, 10, and 24 h; and at V2 after 10 h.

Inspection of figure 3 suggests that epidural morphine

increased the heat pain threshold more profoundly than the heat pain tolerance. However, the variance associated with the heat pain threshold was larger than that associated with the heat pain tolerance (compare magnitude of error bars in fig. 3 and SDs in table 1). To

Fig. 3. The three upper plots display the average change of the heat pain threshold from baseline (\pm SEM) *versus* time at the lumbar (L4), thoracic (T10), and trigeminal (V2) dermatome after epidural administration of morphine and saline placebo, respectively. The three lower plots display corresponding results for the heat pain tolerance. The area under the curve (pain threshold/tolerance *vs.* time) was significantly different between morphine and saline placebo treatments at L4 and T10 when measuring the heat pain threshold. The area under the curve was significantly different at all three dermatomes when measuring the heat pain tolerance ($P < 0.017$, paired t test or Wilcoxon signed rank test with Bonferroni correction). Times at which morphine and saline placebo treatments were significantly different are marked with an asterisk ($P < 0.0125$, paired t test or Wilcoxon signed rank test with Bonferroni correction).

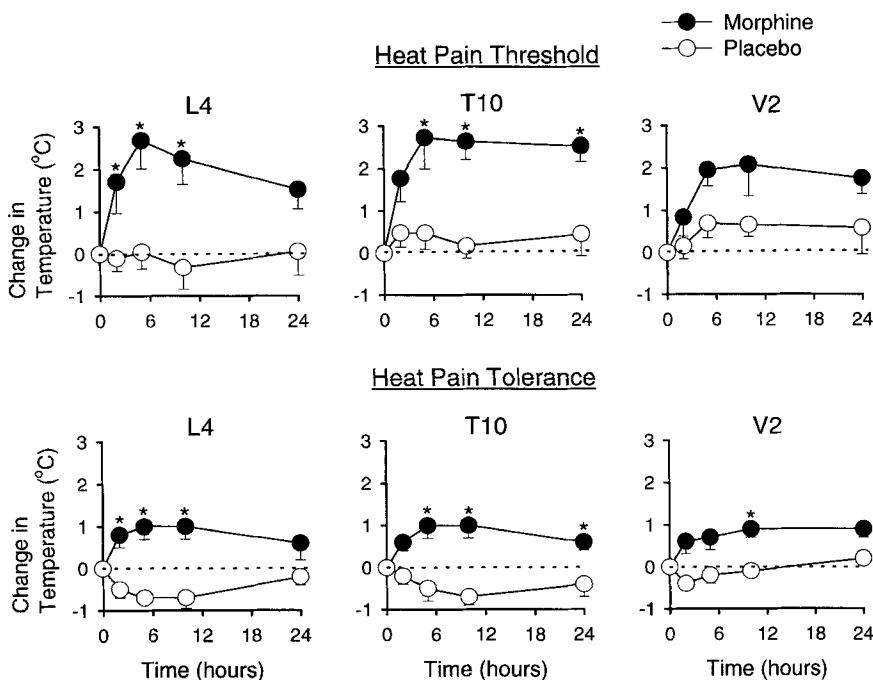


Table 2. Electrical Pain Threshold and Electrical Pain Tolerance at three Dermatomes before and after Lumbar Epidural Administration of 5 mg Morphine and Saline Placebo

	Pain Threshold (mA)		Pain Tolerance (mA)	
	Morphine	Saline Placebo	Morphine	Saline Placebo
Lumbar 4*				
0 h	2.4 ± 1.3	2.4 ± 1.3	7.5 ± 3.1	8.9 ± 3.9
2 h	2.5 ± 1.3	2.0 ± 1.0	8.6 ± 3.5 [†]	7.0 ± 3.2
5 h	3.4 ± 1.4	2.4 ± 1.1	10.4 ± 4.8 [†]	7.3 ± 3.0
10 h	3.6 ± 1.5	2.6 ± 1.2	9.0 ± 3.7 [†]	7.1 ± 3.0
24 h	3.8 ± 2.3	2.5 ± 1.2	9.7 ± 6.4	7.5 ± 3.4
Thoracic 10*				
0 h	2.4 ± 1.4	3.2 ± 1.5	8.5 ± 3.9	9.1 ± 3.8
2 h	2.9 ± 1.2	3.3 ± 1.5	10.7 ± 2.4	8.8 ± 3.5
5 h	3.7 ± 1.3	3.2 ± 1.4	11.7 ± 4.4 [†]	8.5 ± 3.3
10 h	4.1 ± 1.5	3.7 ± 1.6	11.6 ± 4.7 [†]	7.8 ± 3.1
24 h	3.7 ± 2.2	2.8 ± 1.2	10.9 ± 5.9	8.4 ± 3.7
Cervical 2				
0 h	2.2 ± 1.2	2.3 ± 1.3	5.7 ± 2.2	6.3 ± 3.8
2 h	2.0 ± 1.0	2.0 ± 1.0	6.2 ± 1.7	5.2 ± 3.0
5 h	2.4 ± 1.2	1.9 ± 0.9	5.6 ± 1.7	4.6 ± 2.6
10 h	2.3 ± 1.3	2.1 ± 1.4	6.1 ± 2.4	4.8 ± 2.7
24 h	2.6 ± 1.6	2.4 ± 1.7	6.2 ± 2.3	6.3 ± 3.3

Values are mean ± SD.

$P < 0.05$ with Bonferroni correction.

* Epidural injection of morphine and saline placebo resulted in a significantly different AUC describing the percentage change of the electrical pain tolerance from baseline *versus* time. The AUC describing the percentage change of the electrical pain threshold from baseline *versus* time was not significantly different but tended to be larger after epidural injection of morphine.

[†] Times when a significantly different electrical pain tolerance was measured (percentage change from baseline) between epidural injection of morphine and saline placebo.

determine as to which of the two effect measures (pain threshold or pain tolerance) was more suitable to detect morphine-induced analgesia, the detected difference between treatments (morphine *vs.* placebo) needs to be related to associated variance. In other words, not the signal itself (difference between treatments) but the ratio between the signal and associated noise (variance unrelated to treatments) determines how readily an effect measure detects a difference between treatments. One way of relating the so-defined signal to associated noise offers omega-squared statistics.¹⁶ Omega-squared estimates the fraction of the overall variability of the effect measure that can be attributed to the fact that subjects received different treatments (morphine *vs.* saline placebo). Omega-squared associated with the heat pain threshold and the heat pain tolerance were 0.35 and 0.47 at L4, 0.44 and 0.56 at T10, and 0.14 and 0.39 at V2, respectively. It has been suggested that an omega-squared value > 0.15 indicates a large treatment effect.¹⁶ Despite a larger difference between the means of the heat pain threshold after epidural morphine and saline placebo administration, the heat pain tolerance was con-

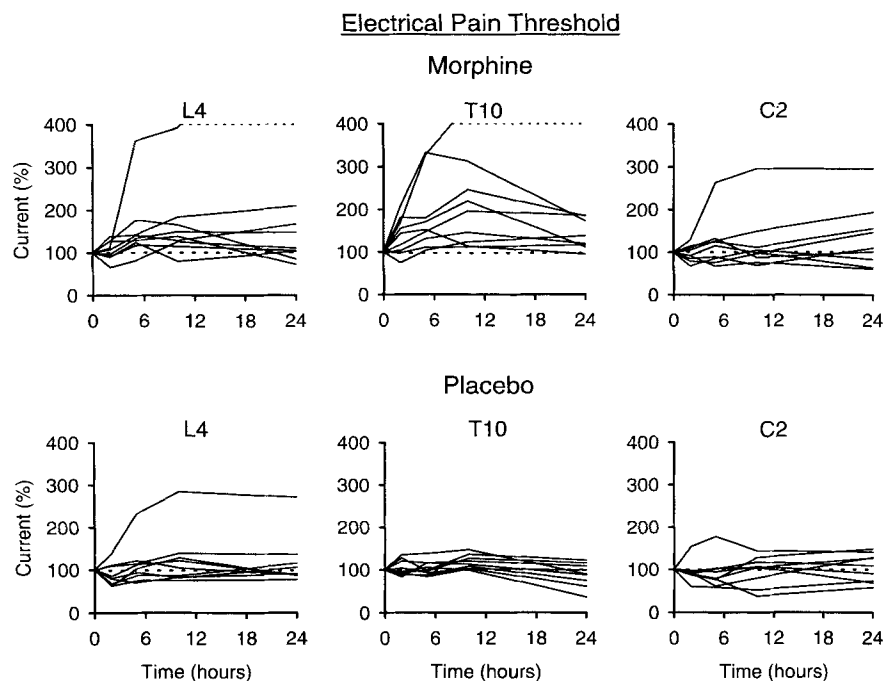
sistently associated with a larger omega-squared, *i.e.*, was more suitable to detect morphine-induced analgesia. This explains why, at the level of V2, the heat pain tolerance was significantly different, but the heat pain threshold was only elevated as a trend when comparing epidural morphine with saline placebo administration.

Electrical Experimental Pain Tests

Table 2 lists the raw values of the electrical pain threshold and the electrical pain tolerance obtained at L4, T10, and C2 before and after epidural administration of morphine and saline placebo, respectively. In contrast, figures 4 and 5 depict individual percentage changes of the electrical pain threshold and the electrical pain tolerance from baseline at L4, T10, and C2 after morphine (top graphs) and saline placebo (bottom graphs), respectively. Figure 6 summarizes the individual data presented in figures 4 and 5, depicting the average percentage change of the electrical pain threshold (top graphs) and the electrical pain tolerance (bottom graphs) from baseline.

The electrical pain threshold increased at L4 and T10 but

Fig. 4. Hairball plots depict individual changes of the electrical pain threshold *versus* time in nine subjects. The three upper plots display the percentage change from baseline at the lumbar (L4), thoracic (T10), and cervical (C2) dermatome after epidural administration of morphine. The three lower plots display the same measurements after epidural injection of saline placebo. A dotted line indicates values exceeding 400%.



hardly changed at C2 after epidural morphine administration. The electrical pain threshold did not change after epidural injection of saline placebo. The electrical pain threshold peaked between 5 and 24 h. Comparing epidural injection of morphine with saline placebo, the AUC describing the percentage change of the electrical pain threshold from baseline *versus* time tended to be larger at L4 and T10 ($P = 0.10$ and 0.02 , respectively) but not at C2.

The electrical pain tolerance increased at L4 and T10 but hardly changed at C2 after epidural morphine administration. The electrical pain tolerance did not change or decreased after epidural injection of saline placebo. The electrical pain tolerance peaked between 2 and 10 h. The AUC describing the percentage change of the electrical pain tolerance from baseline *versus* time was significantly different between epidural morphine and saline injections at L4 and T10 but not at C2 ($P < 0.017$). Comparing epidural morphine with epidural saline injections, the electrical pain tolerance was significantly increased at L4 after 2, 5, and 10 h and at T10 after 5 and 10 h.

Omega-squared associated with the electrical pain threshold and the electrical pain tolerance was determined as outlined for the heat pain data. However, although the same algorithm was used to determine the heat pain threshold and the heat pain tolerance, different algorithms were used to determine the electrical pain threshold and the electrical pain tolerance. This limits interpreting as to which of the electrical pain measures

may generally be more suitable to detect morphine-induced analgesia. The electrical pain threshold and the electrical pain tolerance were associated with omega-squared of 0.23 and 0.30 at T10 and 0.00 and 0.04 at C2, respectively. The omega-squared at L4 was 0.40 for the electrical pain tolerance but could not reliably be determined for the electrical pain threshold because of the skewed distribution of the data.

Morphine Plasma Concentration

Figure 7 shows the average morphine plasma concentration *versus* time after epidural injection. Concentrations were highest after 2 h (first measurement), declining exponentially to less than the detection limit (1 ng/ml) in eight subjects after 10 h.

Adverse Events

After epidural administration of morphine, seven subjects felt nauseated, three vomited, and seven had difficulties voiding during the first 10 h. All subjects reported pruritus up to 24 h. The time course and incidence of side effects are shown in figure 8. After epidural administration of saline, one subject felt nauseated.

Vital Signs

Changes in blood pressure, heart rate, respiratory rate and blood oxygen saturation over time were not differ

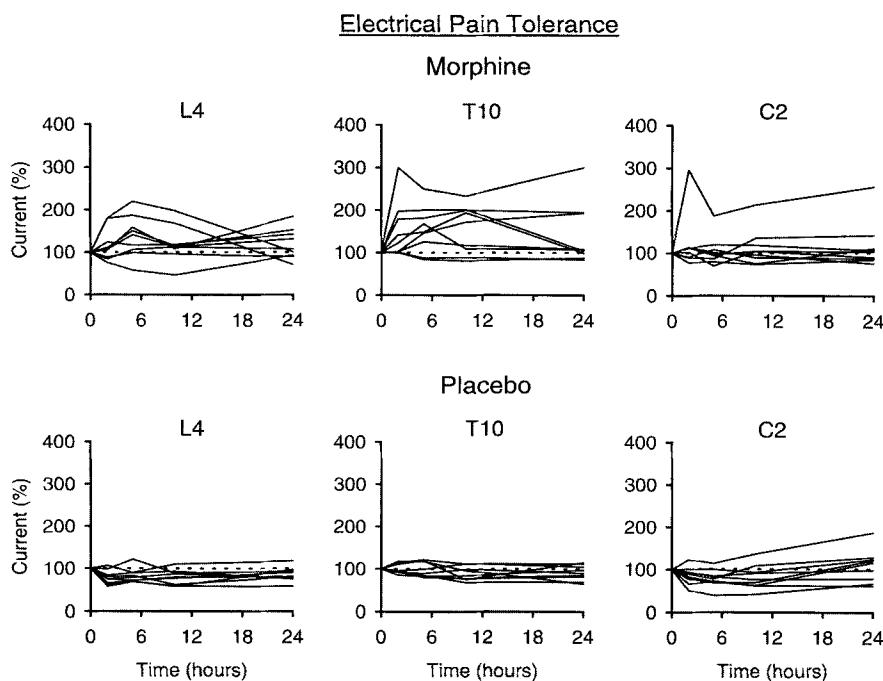


Fig. 5. Hairball plots depict individual changes of the electrical pain tolerance *versus* time in nine subjects. The three upper plots display the percentage change from baseline at the lumbar (L4), thoracic (T10), and cervical (C2) dermatome after epidural administration of morphine. The three lower plots display the same measurements after epidural injection of saline placebo.

ent after epidural morphine or saline injection. Blood pressure and respiratory rate remained within 15%, and heart rate remained within 25% of the baseline value. Changes were most pronounced at night when subjects were asleep.

Discussion

This study reports long-lasting supraspinal analgesic effects to nociceptive heat stimuli after epidural administration of 5 mg morphine, but not after epidural injection of saline placebo.

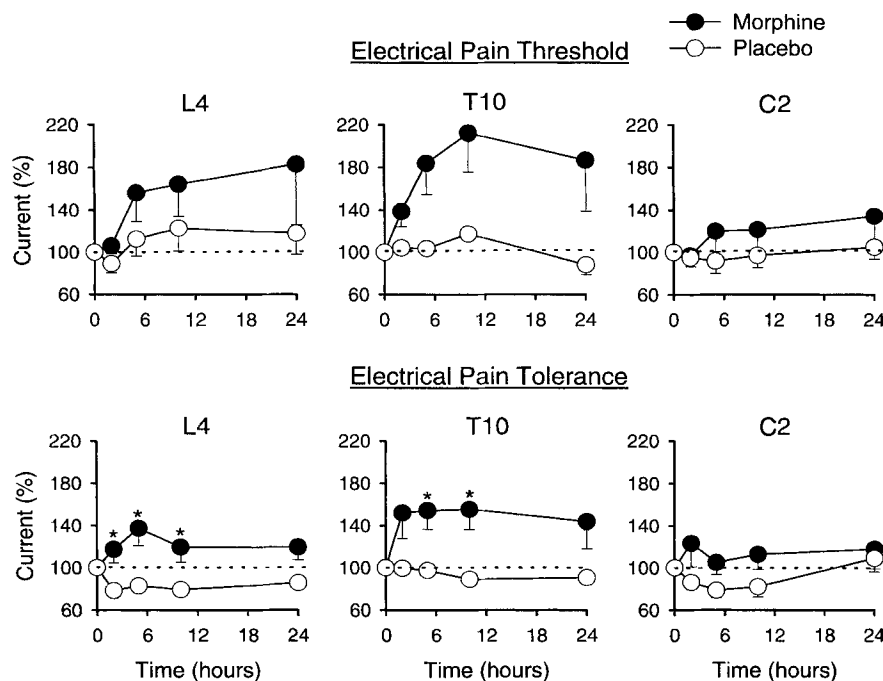


Fig. 6. The three upper plots display the average percentage change of the electrical pain threshold from baseline (\pm SEM) *versus* time at the lumbar (L4), thoracic (T10), and cervical (C2) dermatome after epidural administration of morphine and saline placebo, respectively. The three lower plots display corresponding results for the electrical pain tolerance. The area under the curve (pain tolerance *vs.* time) was significantly different between morphine and saline placebo treatment at L4 and T10 when measuring the electrical pain tolerance ($P < 0.017$, paired *t* test or Wilcoxon signed rank test with Bonferroni correction). Times at which morphine and saline placebo treatments were significantly different are marked with an asterisk ($P < 0.0125$, paired *t* test or Wilcoxon signed rank test with Bonferroni correction).

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tion of saline placebo in the same human volunteers. Significant supraspinal analgesic effects were measured up to 10 h and persisted as a trend for 24 h.

Only few experimental studies have explored the segmental distribution of analgesic effects after lumbar epidural administration of morphine. Bromage *et al.*⁹ described a time-dependent analgesic spread to pin-prick-evoked pain up to supraspinal levels after epidural administration of 10 mg morphine. Other investigators reported a significant, time-dependent analgesic spread to laser-evoked pricking pain up to thoracic but not cervical levels after epidural injection of 4 mg morphine.¹² Finally, two studies reported analgesic effects to pressure-evoked pain at the forehead after lumbar and low thoracic administration of 3–7 mg morphine.^{10,11} However, these analgesic effects were only measured up to 3 h, possibly too short a duration to exclude an uptake into the systemic circulation with subsequent distribution of morphine to the brain as an underlying mechanism. Morphine enters the systemic circulation to a similar extent after epidural and intramuscular injection.^{13–15}

In our study, 5 mg lumbar epidural morphine resulted in prolonged supraspinal analgesia to heat pain. In contrast, previous investigations reported that 10 mg lumbar epidural morphine attenuated pain to pin prick up to the

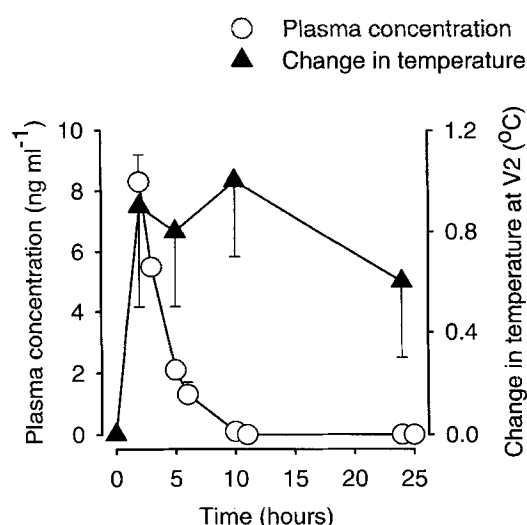


Fig. 7. White circles depict the average plasma concentration (\pm SEM) versus time after epidural injection of morphine. After 10 h, plasma concentrations were less than the detection limit (1 ng/ml) in eight of nine subjects. Black triangles depict the average difference in heat pain tolerance (\pm SEM) between morphine and placebo treatment versus time at the trigeminal dermatome (V2). Plasma concentrations and analgesic effects did not correlate.

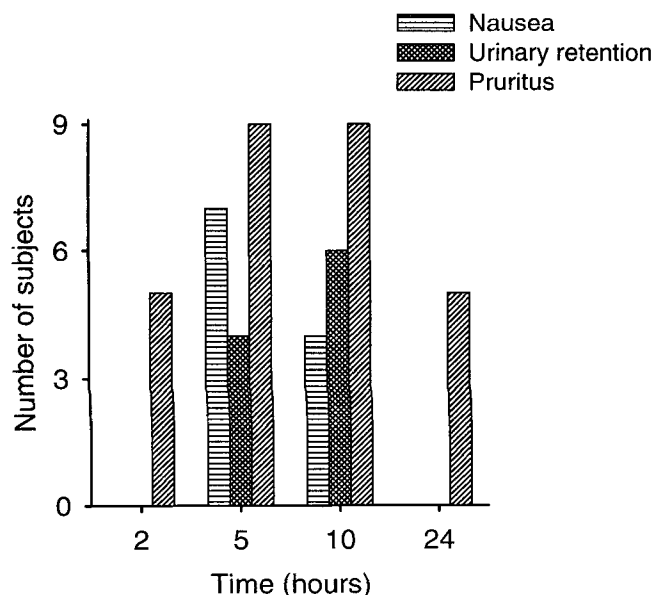


Fig. 8. The incidence and time course of side effects recorded after epidural administration of morphine is displayed. Pruritus preceded and outlasted the occurrence of nausea and urinary retention. The occurrence of pruritus and supraspinal analgesia followed a similar time course. This suggests that epidural morphine may cause supraspinal analgesia at a lower dose than that necessary to evoke nausea.

supraspinal level, but 4 mg lumbar epidural morphine reduced laser-induced pricking pain only up to the thoracic level.^{9,12} In other words, epidural morphine seems to attenuate heat pain more potently or up to a higher dermatomal level than pricking pain. Behavioral and electrophysiologic evidence suggests that morphine blocks C-fiber-mediated pain more potently than A δ -fiber-mediated pain.^{17–20} Behavioral and electrophysiologic evidence also suggests that heat pain is predominantly mediated by C fibers if skin is heated at a slow rate ($< 2^\circ\text{C/s}$).^{17,21–24} On the other hand, pricking pain is thought to be transmitted primarily by A δ -fibers.^{25–27} Therefore, one may speculate that C fibers primarily signaling heat pain were more potently blocked by epidural morphine than A δ fibers signaling pricking pain, and, consequently, heat pain was attenuated up to a higher dermatomal level than pricking pain.

In a clinical context, the presented finding implies that some types of pain may be attenuated up to the supraspinal level after lumbar epidural administration of morphine. The clinical report of successfully attenuating cancer pain in the head and neck region with a lumbar intrathecal infusion of morphine in a selected group of patients is noteworthy.²⁸ All of these patients suffered

from intolerable side effects during previous treatment with systemic opioids.

In our study, significant analgesia was detected for heat pain at the level of the trigeminal nerve but not for electrical pain at a cervical level. In contrast to nociceptive heat consistently evoking a burning pain, electrical pain evoked a mixed pain perception. Subjects reported a sharp or stinging as well as a burning pain component. This indicates simultaneous recruitment of A δ and C fibers in nociceptive signaling.²⁴⁻²⁷ The fact that nociceptive electrical stimuli simultaneously stimulated various types of nerve fibers yielding a different sensitivity to morphine may explain why electrical pain was less potentially blocked than heat pain.¹⁷⁻²⁰

Alternatively, the cervical dorsal horn may not be as sensitive to opioid action as the spinal tract of the trigeminal nucleus involved in processing nociceptive information. After spinal administration of opioids, pruritus, which is reversible by naloxone, is particularly common in the face, *i.e.*, skin areas innervated by the trigeminal nerve.²⁹ This may point to an exquisite sensitivity of the trigeminal nucleus to opioid action. However, the spinal dorsal horn and the trigeminal spinal tract nucleus share a similar neuroanatomic organization, and both are rich in μ -opioid receptors.^{30,31} Future research may clarify if opioid potency varies for different spinal and medullary dermatomes.

Analgesic effects to nociceptive heat stimuli were observed at all tested dermatomes 2 h after administration of epidural morphine, peak effects were recorded between 5 and 10 h, and analgesia lasted the entire 24-h observation period. Highest morphine plasma concentrations were measured 2 h after administration of epidural morphine and were approximately half of the minimal effective plasma concentration necessary for the treatment of postoperative pain.³² Plasma morphine concentrations decreased to less than the detection limit (1 ng/ml) in eight subjects after 10 h. Therefore, the long-lasting analgesic action must have been caused by intraspinal mechanisms and cannot be explained by an initial uptake of morphine into the systemic circulation with subsequent distribution to the brain. Analgesic effects peaking between 2 and 7 h and lasting between 13 and > 24 h have been reported after epidural administration of morphine and were attributed to its spinal action.^{13-15,33}

Traditionally, a pharmacokinetic explanation is given for effects involving the brain stem after epidural administration of morphine. Morphine is absorbed slowly from the epidural space but then quickly spreads rostrally and

becomes detectable in cervical cerebrospinal fluid after 60 min.^{6,7,33-35} Significant morphine concentrations in cerebrospinal fluid at the brain stem are considered to cause side effects such as facial pruritus, nausea, or sedation.^{8,29} More recently, an alternative pharmacodynamic explanation suggested that it is the opioid effect and not the drug itself that spreads rostrally, thereby triggering various supraspinal effects.^{36,37} Modulating opioid action at the spinal cord causing differential activity of various ascending pathways has been a suggested mechanism for facial pruritus.³⁶ Spinal opioids blocking ascending pathways that are tonically inhibiting supraspinal antinociceptive mechanisms has been suggested as a mechanism to explain supraspinal antinociceptive action.³⁷

Our study does not allow differentiation between the pharmacokinetic and the pharmacodynamic model. However, a dose-response relationship seems evident for the rostral spread of analgesic effects, making the pharmacokinetic explanation appealing.^{9,12} Clearly, more research is necessary to evaluate the relative importance of pharmacokinetic and pharmacodynamic mechanisms that result in supraspinal opioid action after epidural administration.

The time course observed for the incidence of pruritus and nausea is in agreement with previous reports.^{8,38,39} Pruritus preceded and outlasted the occurrence of nausea. The time courses of pruritus and measured supraspinal analgesia were similar. This suggests that smaller doses of epidural morphine are necessary for causing supraspinal analgesic effects on heat pain than for causing nausea.

Compared with baseline, the heat and electrical pain tolerance typically were lower 2, 5, and 10 h after epidural injection of saline placebo but returned close to baseline after 24 h. This observation was not made when measuring the pain threshold. Although our study is not conclusive, several hypotheses about the mechanism underlying this observation can be formulated. First, injection of epidural saline may have caused hyperalgesia to strong nociceptive stimuli. However, it is more likely that injection of epidural saline has a local anesthetic effect if it has an effect at all.⁴⁰ Second, repetitive administration of strong nociceptive stimuli may have caused hyperalgesia. However, such a phenomenon was not observed by other investigators who repetitively assessed the heat and electrical pain tolerance.⁴¹ Third, observed within-day fluctuation of the pain tolerance may be caused by a circadian change in pain sensitivity that does not become apparent when measuring the

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pain threshold. A study investigating the circadian sensitivity of experimentally induced headache found significant fluctuations for intense but not mild pain.⁴² Animal studies suggest that the sensitivity to nociceptive stimuli is lowest at the end of a resting period (dark cycle) and highest at the end of an activity period (light cycle).⁴³ This matches the time course of observed changes in heat and electrical pain tolerance and suggests that the time-dependent variation is not caused by psychologic factors only.

In summary, this study reports long-lasting supraspinal analgesia to heat pain after a lumbar epidural dose of 5 mg morphine. Taken together with data from previous studies, it seems that morphine-mediated analgesic effects on heat pain spread more rostrally than analgesic effects on pricking or electrical pain. In a clinical context, this finding implies that epidural morphine may attenuate various types of pain up to a different dermatomal level.

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