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Neuraxial Morphine May Trigger Transient Motor Dysfunction after a Noninjurious Interval of Spinal Cord Ischemia

A Clinical and Experimental Study

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Background: **A patient underwent repair of a thoracoabdominal aortic aneurysm. Epidural morphine, 4 mg, was given for pain relief. After anesthesia, the patient displayed lower extremity paraparesis. This effect was reversed by naloxone. The authors sought to confirm these observations using a rat spinal ischemia model to define the effects of intrathecal morphine administered at various times after reflow on behavior and spinal histopathology.**

Methods: **Spinal cord ischemia was induced for 6 min using an intraaortic balloon. Morphine or saline, 30 μg, was injected intrathecally at 0.5, 2, or 24 h after reflow. In a separate group, spinal cord temperature was decreased to 27°C before ischemia. After ischemia, recovery of motor function was assessed periodically using the motor deficit index (0 = complete recovery; 6 = complete paraplegia).**

Results: **After ischemia, all rats showed near-complete recovery of function by 4–6 h. Intrathecal injection of morphine at 0.5 or 2 h of reflow (but not at 24 h) but not saline caused a development of hind limb dysfunction and lasted for 4.5 h (motor deficit index score = 4–6). This effect was reversed by intrathecal naloxone (30 μg). Intrathecal morphine administered after hypothermic ischemia was without effect. Histopathological analysis in animals that received intrathecal morphine at 0.5 or 2 h after ischemia (but not at 24 h) revealed dark-staining α motoneurons and interneurons. Intrathecal saline or spinal hypothermia plus morphine was without effect.**

Conclusions: **These data indicate that during the immediate reflow following a noninjurious interval of spinal ischemia, intrathecal morphine potentiates motor dysfunction. Reversal by naloxone suggests that this effect results from an opioid receptor–mediated potentiation of a transient block of inhibitory neurons initiated by spinal ischemia.**

NEURAXIAL delivery of μ-opioid agonists produces potent analgesia in humans and animals.[1] This effect is mediated at the spinal level by the activation of opioid receptors, which are presynaptic and postsynaptic to the primary afferent C fibers. The net inhibitory effect of this activation results from a reduction in the opening of voltage-sensitive calcium channels leading to a reduced transmitter release and by a hyperpolarization of target cells through increased potassium permeability.[2] Opioid binding is also found in the ventral horn and is present on interneurons and α motoneurons. Morphine can produce a reduction in recurrent α-motoneuron inhibition (mediated by Renshaw cells) after systemic injection (5–10 mg/kg intravenous).[3] In the hippocampal CA1 region, treatment with morphine provided a comparable suppression of γ-aminobutyric acid (GABA)–mediated inhibitory interneurons resulting in an increased excitability of pyramidal cells.[4,5] Consistent with these effects on inhibitory interneurons, behavioral studies in rats show that systemic or intrathecal administration of relatively high doses of morphine triggers myoclonic seizures, loss of motor coordination or truncal rigidity,[6,7] or the development of prominent but transient allodynia in rats.[8] In humans, intrathecal morphine has also been shown to yield myoclonus.[9,10] While the mechanism of this is not certain, the results are typically observed after continued exposure to high intrathecal doses.

Previous clinical studies have shown a moderate hemiparesis resulting from spasm of the anterior and middle cerebral artery. The hemiparesis was exacerbated by intravenous morphine (5 mg) and is reversed by naloxone.[11] In a subsequent experimental study using middle cerebral artery occlusion in baboons, a comparable effect was demonstrated when treatment with 15 mg/kg morphine converted upper extremity hemiparesis to hemiplegia. This effect was also reversed by naloxone.[12] Similarly, in a recent clinical experience (see Appendix for details), a patient underwent repair of an extensive thoracoabdominal aortic aneurysm in combination with intraoperative epidural cooling. Epidural morphine, 4 mg, was given during the operation for postoperative pain. The patient awoke with a paraparesis of the lower extremities, which was immediately reversed with a narcotic antagonist.

The motor dysfunction observed after a period of spinal ischemia (aortic cross clamping) and neuraxial morphine administration may result from an exaggerated block of inhibitory neuron function initiated by transient

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spinal ischemia. The temporal profile of such a morphine-induced motor dysfunction after spinal ischemia is not known. In addition, it is not known whether such morphine-induced effect after short-lasting noninjurious intervals of ischemia may potentiate neuronal degeneration and loss of neurologic function which otherwise would only develop after longer ischemic intervals. It is interesting to note that in patients with chronic spinal injury leading to spasticity, spinal morphine can diminish the elevated motor tone.[13] These results thus suggest a differential effect on motor function of spinal opioid receptor activation in acutely challenged as compared to chronically injured spinal cord.

Based on the clinical presentation described above (see Appendix for details), the effects of intrathecal morphine in a well-defined rat model of aortic occlusion associated with spinal cord ischemia were examined. In addition, the effect of selective intraischemic spinal cord hypothermia (27°C), if combined with intrathecal morphine treatment, was studied.

Material and Methods

Experimental animal studies were performed according to protocols approved by the Institutional Animal Care and Use Committee of the University of California, San Diego.

General Animal Preparation

Male Sprague-Dawley rats (300–450 g) were anesthetized with 2.5% halothane in a room air–oxygen mixture (1:1), and lumbar intrathecal catheters (PE-10) were inserted 8.5 cm caudally through the cisternal membrane in the intrathecal space to the rostral edge of the lumbar enlargement.[14] Rats were allowed to recover for a minimum of 2–3 days prior to induction of ischemia. Rats showing motor weakness or sign of paresis on recovery from anesthesia were euthanized.

Induction of Spinal Cord Hypothermia

Details of the subcutaneous cooling technique have been previously reported.[15,16] In brief, a heat exchanger constructed from metal tubing was inserted on the back in a subcutaneous tunnel extending from S2 to upper thoracic (T4–T5) spinal segments. To induce spinal cord hypothermia, water (8–9°C) was perfused through the heat exchanger at 100 ml/min. To control and maintain the degree of spinal cord hypothermia, a thermocouple for the measurement of paravertebral muscle temperature was placed below the heat exchanger, and the output was used to trigger the heat exchanger pump in an on–off fashion using an external microprocessor-based temperature controller. In previous work with this technique, we demonstrated that intrathecal temperature as measured by a thermocouple placed on the dorsal or ventral spinal cord surface could be decreased to 27°C with a 2–3°C temperature gradient measured between the dorsal and ventral surfaces of the lumbar spinal cord. In the current experiment, spinal cord temperature was decreased to 27°C before induction of 6 min of spinal ischemia. In control animals, spinal cord temperature was decreased to 27°C; however, spinal ischemia was not induced.

Induction of Spinal Ischemia

Details of the induction of spinal ischemia have been reported.[17] In brief, animals previously implanted with intrathecal catheters were anesthetized with 4% halothane in room air and maintained with 1–2% halothane delivered by mask. For monitoring of distal arterial pressure and injection of heparin, a polyethylene catheter (PE-50) was inserted into the tail artery. A left femoral artery was isolated, and a 2-French Fogarty catheter was placed into the descending thoracic aorta so that the tip of the catheter reached the level of the left subclavian artery. To control the proximal arterial blood pressure (*i.e.*, above the level of aortic occlusion) at 40 mmHg during the period of aortic occlusion, a 20-gauge Teflon catheter connected to an external blood reservoir (37.5°C) was inserted into the left carotid artery. In the previous study, we have demonstrated that by decreasing proximal arterial pressure to 40 mmHg, it is possible to achieve a consistent and well-controlled decrease in spinal cord blood flow (< 5% of baseline flow) during the period of aortic occlusion.[17]

At completion of cannulation, heparin (200 U) was injected into the tail artery. To induce spinal ischemia, the balloon catheter was inflated with 0.05 ml saline, and the blood was allowed to flow to the external reservoir. The efficiency of the occlusion was evidenced by an immediate and sustained loss of any detectable pulse pressure and drop of distal arterial pressure in the tail artery. After ischemia, the balloon was deflated, and the blood was reinfused during 60 s. Protamine sulfate, 4 mg, was then administered subcutaneously. Arterial lines were removed, incisions were closed, and the rats were allowed to recover from anesthesia. In sham-operated rats, all surgical procedures were performed as described; however, the balloon catheter was not inflated. In all experimental groups, including the sham-operated control group, the duration of anesthesia ranged between 25 and 30 min.

Experimental Groups and Design

There were four major components to the investigation:

Study 1: Assessment of the effect of intrathecal morphine (30 μg) on the neurologic outcome after 6 min of aortic occlusion

Group 1A (n = 8): Control—intrathecal saline injection (10 μl) at 30 min of reperfusion

Group 1B (n = 9): Intrathecal injection of morphine at 30 min of reperfusion

Group 1C (n = 5): Sham-operated animals—intrathecal injection of morphine at 30 min after recovery from anesthesia

Study 2: Assessment of the effect of intrathecal naloxone (30 μg) on morphine (30 μg)–induced motor dysfunction after 6 min of aortic occlusion

Group 2A (n = 6): Intrathecal morphine injection at 30 min of reflow followed by saline injection at 2.5 h

Group 2B (n = 6): Intrathecal morphine injection at 30 min of reflow followed by naloxone injection at 2.5 h

Group 2C (n = 6): Control—Intrathecal saline injection at 30 min and 2 h after ischemia

Study 3: Increasing intervals of postischemic reflow and the potency of intrathecal morphine (30 μg) in inducing motor dysfunction after 6 min of aortic occlusion

Group 3A (n = 9): Intrathecal morphine injection 30 min after ischemia

Group 3B (n = 6): Intrathecal morphine injection 2 h after ischemia

Group 3C (n = 6): Intrathecal morphine injection 24 h after ischemia

Study 4: Effect of intraischemic hypothermia (27°C) and the potency of intrathecal morphine (30 μg) in inducing motor dysfunction after 6 min of aortic occlusion

Group 4A (n = 6): Intrathecal morphine injection 30 min after hypothermic ischemia

Group 4B (n = 6): Nonischemic control—intrathecal morphine injection 30 min after spinal hypothermia

Assessment of Neurologic Function

Neurologic function was assessed periodically (at 30 min, 1 h, 2 h, 4.5 h, 8.5 h, 24 h, and 48 h) after ischemia, hypothermia, and/or drug treatment using the following grading system: Motor function was quantified by assessment of ambulation and placing and stepping responses. For statistical purposes, ambulation (walking with lower extremities) was graded as follows: 0 = normal; 1 = toes flat under the body when walking but ataxia present; 2 = knuckle walking; 3 = movement in lower extremities but unable to knuckle walk; or 4 = no movement; drags lower extremities. Dragging the dorsum of the hind paw over the edge of a surface assessed the placing/stepping reflex. This normally evokes a coordinating lifting and placing response (*e.g.*, stepping), which was graded as follows: 0 = normal; 1 = weak; 2 = no stepping. A motor deficit index (MDI) score was calculated for each rat at each time interval. The final MDI was the sum of the scores (walking with lower extremities plus placing and stepping reflex; MDI of 0 = complete recovery; MDI of 6 = complete paraplegia).

Perfusion Fixation and Histopathological Analysis

At the end of the survival period (*i.e.*, 48 h after drug treatment), rats were terminally anesthetized with pentobarbital (100 mg/kg intraperitoneal) and phenytoin (25 mg/kg intraperitoneal). The rats were then transcardially perfused with 100 ml heparinized saline followed by 150 ml paraformaldehyde, 4%, in phosphate buffer (pH = 7.4). Twenty-four hours later, the spinal cords were removed and postfixed in the same fixative for 2–14 days. After this period, the spinal cords were removed, and L3, L4, and L5 spinal segments were dissected and cryoprotected in 30% sucrose solution. Frozen transverse sections (20–30 μm) were then prepared and stained with Kluver-Barrera method. In selected animals, a portion of the spinal cord tissue was postfixed in 1% buffered OsO4 and embedded in high-viscosity epoxy resin (Araldite; Polysciences, Inc., Warrington, PA). Semithin sections (1-μm thick) were prepared and stained with p-phenylenediamine. For systematic analysis, 10 representative sections taken form each L3–L5 segment (total of 30 sections from each spinal cord) were coded in each animal and then subjected to a systematic examination. Scores were tabulated and prepared for analysis by the observer without knowledge of the treatment group (M. K.).

Drugs and Injection

Drugs were obtained as follows: morphine sulfate (Merck, Whitehouse Station, NJ), naloxone HCl (DuPont Pharm., Wilmington, DE). Agents were dissolved for injections with saline. Doses for spinal delivery were prepared to be delivered in a volume of 10 μl. Each intrathecal injection was followed by an injection of 10 μl saline to flush the catheter.

Statistics

Statistical analyses of physiologic data were performed by one-way analysis of variance for multiple comparisons followed by Dunnett *post hoc* test. For the analysis of neurologic outcome and spinal histopathology, nonparametric tests were used. For each individual study (study 1, study 2, study 3), tests for overall main effects were performed with the Kruskal-Wallis test. Significant main effects ($P < 0.05$) were probed further through sequential comparisons of each test condition to the adjacent test condition (*e.g.*, morphine injection at 30 min, 120 min, or 24 h after reflow) using the comparison of experimental Mann–Whitney test (unpaired two-group test). To correct for the increased probability of type I error with multiple comparisons, our significance level for *post hoc* Mann–Whitney test comparisons was set at $P = 0.01$. Data were expressed as mean ± SD.

Results

Preischemic and Intraischemic Observations

During the preischemic and intraischemic periods, body temperature ranged between 38.4 and 37.2°C. Baseline distal arterial pressure was 82 ± 12 mmHg and decreased to 5 ± 3 mmHg at the end of 6 min of aortic occlusion. No significant differences between experimental groups were detected.

Study 1: Effect of Intrathecal Morphine on Outcome after Aortic Occlusion

Group 1A: Control—Intrathecal Saline Injection at 30 Minutes of Reperfusion. All rats showed modest and transient motor weakness (MDI = 2–3) at 30 min after reperfusion followed by gradual recovery over a 24- to 48-h period of reflow (fig. 1). During the initial 0.5–8.5 h after ischemia, motor deficit was expressed as the presence of ataxia (but with preserved ability to walk) and partial weakness in place-stepping reflex. At 48 h, no significant motor deficit was seen. All rats showed complete recovery, which was comparable with sham-operated animals (group 1C). Intrathecal saline at 30 min of reperfusion had no detectable effect on continuing recovery of motor function.

Group 1B: Intrathecal Morphine (30 μg) at 30 Minutes of Reperfusion. Intrathecal injection of morphine resulted in a gradual development of motor dysfunction and near-complete loss of the ability of rats to stand, walk, or step (fig. 1). Only partial movement of lower extremities or knuckle walking was seen. The peak of morphine-induced effect was observed between 60–120 min after morphine administration ($P < 0.01$) and persisted through 4–5 h ($P < 0.05$). Between 24 and 48 h after injection, the majority of animals regained motor function. At 48 h, one animal showed continuing presence of motor deficit (MDI = 4).

Group 1C: Sham Operation Plus Intrathecal Morphine (30 μg). In sham-operated animals, intrathecal morphine had no effect on neurologic function, and all rats showed near-normal ambulation after recovery from anesthesia (fig. 1).

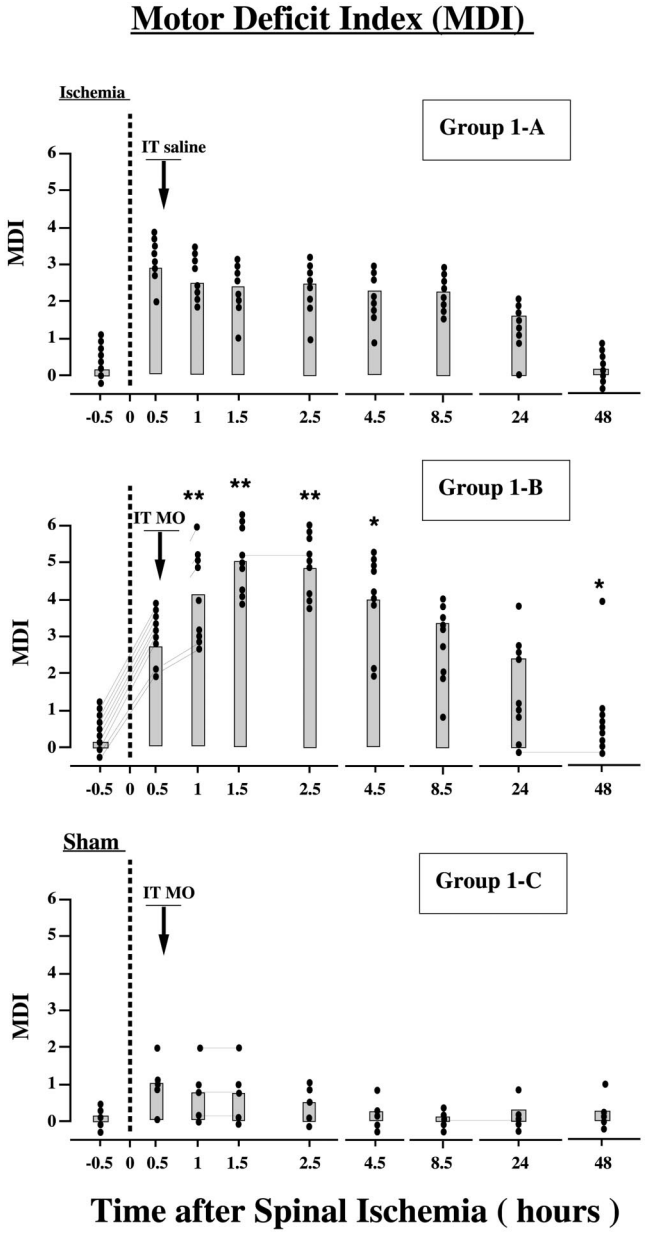

Fig. 1. Motor deficit index assessed at 30 min to 48 h in animals after sham operation (group 1C) or 6 min of aortic occlusion and intrathecal injection of saline (group 1A) or 30 μg morphine (group 1B). A significant motor dysfunction–inducing effect of intrathecal morphine when administered after ischemia can be seen ($P < 0.01$, *$P < 0.05$, compared to group 1A).**

Study 2: Effect of Intrathecal Morphine followed by Naloxone on Outcome after Aortic Occlusion

Group 2A: Control—Intrathecal Saline 2 Hours after Intrathecal Morphine (30 μg). Intrathecal saline had no significant effect on ischemia-morphine–induced spasticity, and all animals displayed comparable time courses of spastic paraplegia as described in group 1B (fig. 2).

Group 2B: Intrathecal Naloxone (30 μg) 2 Hours after Intrathecal Morphine (30 μg). Intrathecal naloxone at 90 min after morphine injection (*i.e.*, during the peak of morphine-induced motor dysfunction) led to a reversal of motor dysfunction (fig. 2). The majority of these rats regained their ability to walk and step 30 min after intrathecal naloxone ($P < 0.01$).

Group 2C: Intrathecal Saline at 30 Minutes and 2.5 Hours after Reflow. Repetitive intrathecal saline had no effect (fig. 2). All rats showed comparable motor recovery profiles as seen after single saline injection (*i.e.*, group 1A).

Study 3: Increasing Intervals of Postischemic Reflow and Effect of Intrathecal Morphine

Group 3A: Intrathecal Morphine Injection (30 μg) at 30 Minutes after Reflow. This experimental group was not different in any respect from group 1B (fig. 3).

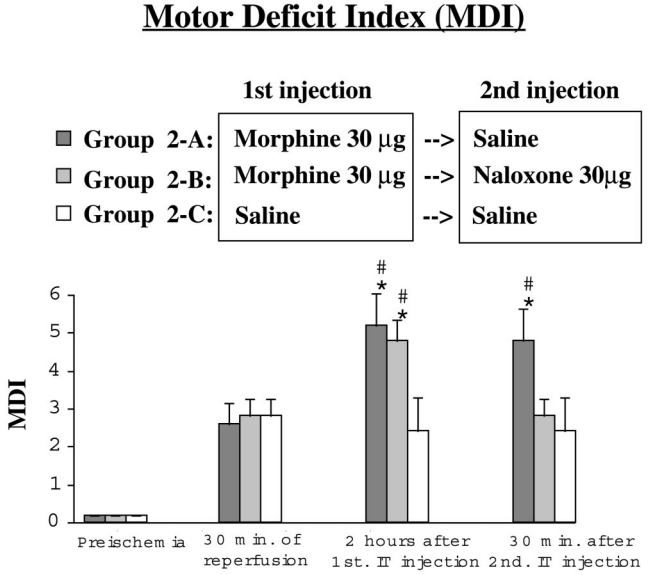

Fig. 2. Effect of intrathecal naloxone treatment on morphine-induced motor dysfunction after 6 min of spinal ischemia. Note a complete reversal of morphine-induced motor deficit at 30 min after naloxone administration (*#P < 0.01, *compared to group 2B, #compared to group 2C).

Group 3B: Intrathecal Morphine (30 μg) at 2 Hours or Reflow. Intrathecal morphine at 2 h after reflow evoked comparable development of motor dysfunction as observed after morphine administration at 30 min of reperfusion (fig. 3). The peak effect was observed between 60 and 120 min after morphine injection when the majority of animals showed significant loss of their ability to walk or to stand. Statistical analysis showed no difference between morphine-induced effects observed at 30 or 120 min after spinal ischemia. At 24 h, four of six rats regained their ability to walk and step. Two rats showed persisting signs of motor dysfunction, which partially disappeared at 48 h after reflow.

Group 3C: Intrathecal Morphine (30 μg) at 24 Hours after Reflow. Intrathecal morphine at 24 after ischemia had no significant effect as compared with control saline-injected animals (fig. 3).

Study 4: Effect of Intraischemic Hypothermia (27°C) and Effect of Intrathecal Morphine

Group 4A: Intrathecal Morphine (30 μg) and Hypothermic Ischemia. No effect on motor function after intrathecal morphine was seen, and all animals showed similar neurologic profiles, as seen in control normothermic, nonischemic animals (see group 1C).

Group 4B: Control—Intrathecal Morphine (30 μg) 30 Minutes after Spinal Hypothermia. Similarly, in this group, no detectable effect on neurologic function was seen.

Histopathological Analysis

Study 1 (Groups 1A and 1C). Systematic histopathological analysis of L2–L5 spinal segments at the end of

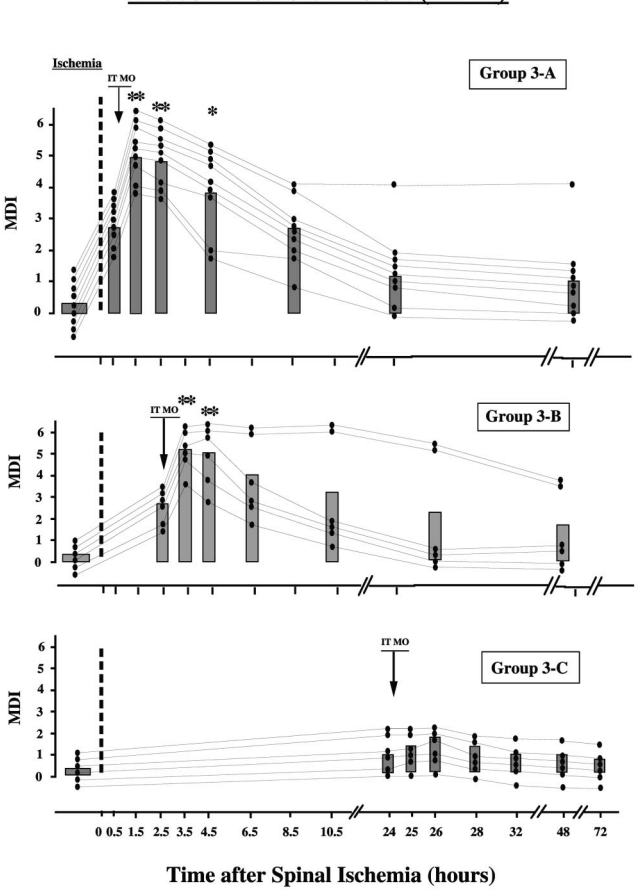

Fig. 3. Motor deficit index assessed at 30 min to 72 h in animals after 6 min of spinal ischemia followed by intrathecal injection of morphine at 30 min (group 3A), 2 h (group 3B), or 24 h (group 3C). Note a significant motor dysfunction–potentiating effect of intrathecal morphine if administered at 30 min or 2 h (but not at 24 h) after ischemia (P < 0.01, *P < 0.05).**

48 h of survival showed no detectable neurodegenerative changes. All neuronal pools, including small- and medium-sized interneurons and large α motoneurons, showed normal structure with well-preserved neuronal membrane, nucleus, and nucleolus. Similarly, no apparent degenerative changes in the neuropil were observed. In contrast, in group 1B (intrathecal morphine injection at 30 min of reflow), histopathological analysis of spinal cords revealed occasional presence of dark-staining α motoneurons and medium-sized interneurons localized in ventral and dorsal horn in lumbosacral segments (figs. 4A and B).

Study 2 (Group 2B). Intrathecal naloxone at 2 h after morphine administration had no apparent effect on the occurrence of dark-staining neurons, and a comparable number of dark-staining neurons localized in the ventral and dorsal horn in lumbosacral segments were seen (table 1).

Study 3 (Group 3C). In rats injected with intrathecal morphine (30 μg) at 24 h after 6 min of spinal ischemia,

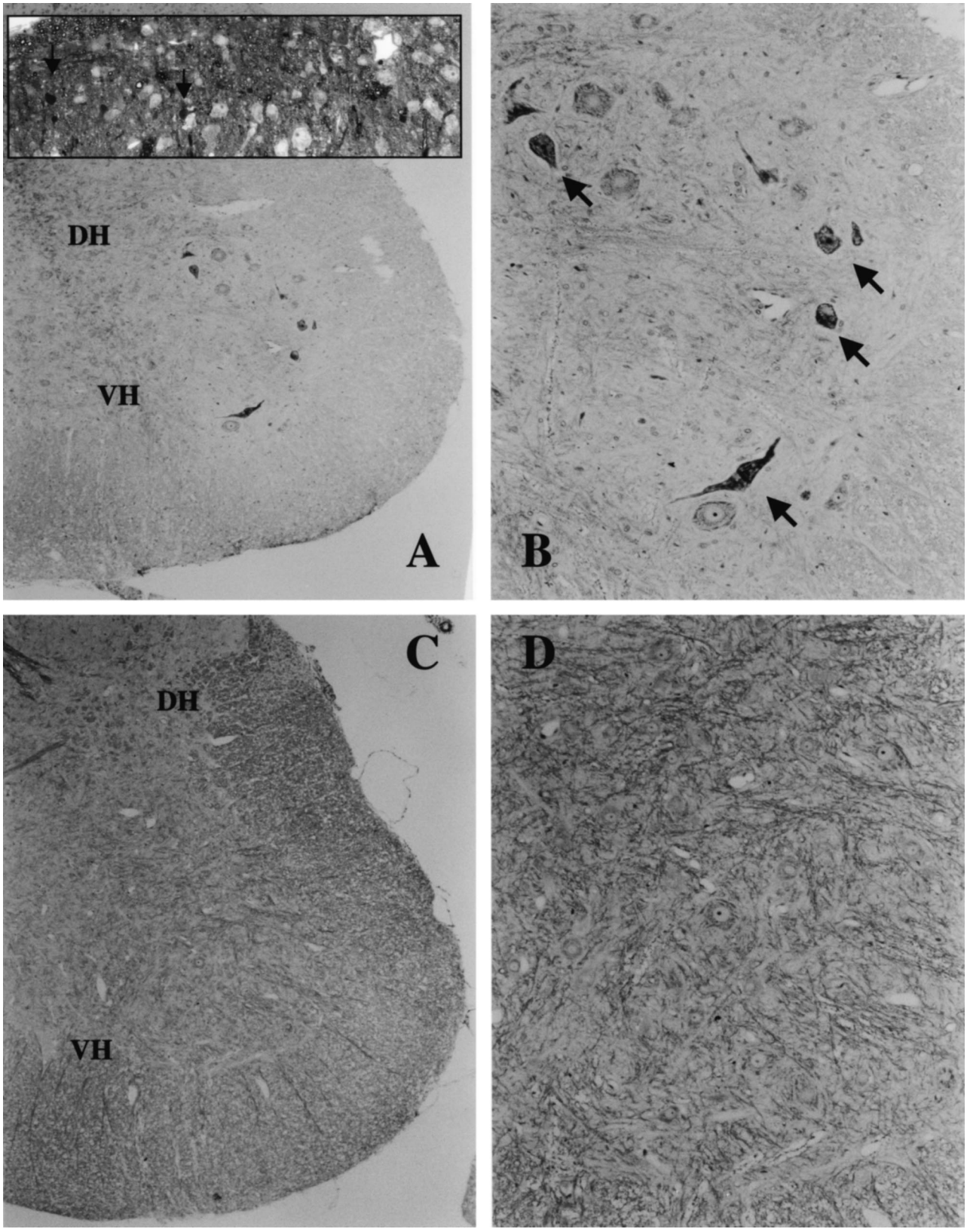

Fig. 4. (*A*, *B*) Light microphotograph of the transverse (1 or 30 μm) section taken from L3 spinal segment of an animal subjected to 6 min of spinal ischemia and 48 h of reperfusion. Animal received 30 μg intrathecal morphine at 30 min of reflow. Number of dark-staining α motoneurons (arrows) localized in ventral horn and in dorsal horn (*A*, *inset*, arrows; 40×) can be seen (original magnification 10× [*A*], 20× [*B*]. (*C*, *D*) Light microphotograph of the transverse (30 μm) section taken from L3 spinal segment of an animal subjected to 6 min of spinal ischemia and 48 h of reperfusion. Animal received 30 μg intrathecal morphine at 24 h of reflow. Normally appearing α motoneurons and interneurons can be seen (original magnification 10× [*C*], 20× [*D*]).

Table 1. Laminar and Segmental Distribution of Dark Staining Neurons in All Experimental Groups

Experimental Group No.	L3	L4	L5
	DH/VH	DH/VH	DH/VH
Study 1			
Group 1-A	1 ± 0.1/2 ± 1	2 ± 1/0	2 ± 0.6/0
Group 1-B	32 ± 8/6 ± 4*	67 ± 11/12 ± 6*	45 ± 22/10 ± 2*
Group 1-C	0/0	0/0	0/0
Study 2			
Group 2-A	26 ± 11/5 ± 2	57 ± 9/7 ± 4	36 ± 7/8 ± 4
Group 2-B	29 ± 8/11 ± 4	49 ± 11/5 ± 2	40 ± 9/11 ± 2
Group 2-C	2 ± 0.1/0	3 ± 0.3/1 ± 0.2	1 ± 0.2/0
Study 3			
Group 3-A	32 ± 8/6 ± 4	67 ± 11/12 ± 6	45 ± 22/10 ± 2
Group 3-B	27 ± 7/8 ± 3	70 ± 9/14 ± 4	40 ± 14/12 ± 4
Group 3-C	4 ± 0.3/2 ± 1	4 ± 1/2 ± 0.6	2 ± 1/1 ± 0.6
Study 4			
Group 4-A	0/0	0/0	0/0
Group 4-B	0/0	0/0	0/0

Each number represents an average (± SD) of dark staining neurons counted in 10 subserial sections in each L3, L4, or L5 segment.

* $P < 0.05$; compared with saline-injected animals.

DH = dorsal horn; VH = ventral horn.

only occasional or no dark-staining neurons were detected at any segmental or laminar level (figs. 4C and D).

Study 4 (Groups 4A and 4B). No detectable histopathological changes were seen in any segmental or laminar level.

Discussion

In the rat study, we sought to address issues raised by the clinical case that was outlined above using a well-defined rat model of transient spinal ischemia coupled with intrathecal drug delivery and spinal cord cooling. In previous work using this spinal ischemia model, we showed that ischemic intervals of 8 min or less are associated with only transient motor dysfunction observed during the initial 60–90 min after reflow. After longer intervals of ischemia (10–12 min), development of spastic or flaccid paraplegia is reliably seen.[17] Histopathological analysis of the spinal cord taken between 8 and 48 h after reflow shows no degenerative changes after 6 min of ischemia, while, in contrast, after ischemic intervals longer than 10 min, selective degeneration of small interneurons localized in the intermediate zone is seen as soon as 8 h after reflow. Such a selective interneuronal degeneration was also seen in several other spinal ischemia models including dog, rabbit, or cat, suggesting the presence of a significant homology across these species.[18–21]

Similarly, as observed in the clinical case, a single injection of an analgesic dose of intrathecal morphine (30 μg) but not saline, after 30 min or 2 h but not 24 h of reflow, resulted in motor dysfunction that lasted for 2–4.5 h in the rat. This duration corresponded to the typical time course of spinally administered morphine in the rat.[22] Intrathecal naloxone given at 2 h (*i.e.*, during the period of fully developed motor dysfunction) completely reversed the motor effect. These observations suggest that transient events within the interval after transient ischemia may render the animal sensitive to the motor dysfunction–inducing effects of a spinal μ opioid.

Histopathological analysis of the spinal lumbosacral segments at 48 h after ischemia–morphine treatment revealed the presence of occasional dark-staining α motoneurons and medium-sized interneurons if morphine was administered at 30 min or 2 h after ischemia (but not when administered at 24 h). Similarly, in control saline-injected rats, no dark-staining neurons were seen. Although the pathologic significance of the presence of dark-staining neurons is not clear, several spinal ischemia studies show that these changes may represent predegenerative changes leading later to irreversible neuronal degeneration.[23–25] Similar occurrence of dark-staining neurons and loss of GABA immunoreactivity in the dorsal horn after chronic constrictive nerve injury was reported.[26] Nonetheless, in the current study, the presence of dark-staining neurons was *not* associated with the presence of motor dysfunction at the time of animal sacrifice. Whether or not repetitive intrathecal or epidural administration of morphine after transient spinal ischemia can trigger neuronal degeneration is not known.

Mechanism of Morphine-induced Spasticity after a Noninjurious Interval of Spinal Ischemia

In previous experimental studies, we demonstrated that after periods of transient spinal ischemia sufficient to produce spastic paraplegia, there is a selective degeneration of small- and medium-sized interneurons typically localized between laminae V and VII.[17,20,23] Although the transmitter phenotype of these neurons is not known, a significant spasticity-alleviating effect of

intrathecal baclofen ($GABA_B$ receptor agonist) suggests that these neurons are likely of GABA and/or glycinergic origin.[27] Accordingly, biochemical analysis of the spinal cord gray matter in lumbar segments in animals with fully developed spastic paraplegia showed a significant decrease in tissue content of glycine and GABA in the cat.[21] In addition, there is a significant loss of polysynaptic inhibitory spinal cord evoked potentials and an increase in monosynaptic reflex in rats with chronic spasticity.[19]

As discussed previously, systemic administration of high-dose (5–10 mg/kg intravenous) morphine causes reduction in recurrent α motoneuronal inhibition, mediated by Renshaw cells, in the spinal cord.[3] Similarly, systemic or intrathecal administration of relatively high doses of morphine (300–500 μg) in the rat triggers myoclonic seizures, loss of motor coordination or truncal rigidity,[6,7] or the development of prominent allodynia.[8] Taken together, these data suggest that transient loss of spinal inhibition, initiated by short-lasting spinal ischemia, is further potentiated by opioid receptor activation and is clinically expressed as α motoneuronal disinhibition and a corresponding loss of motor function. It is important to note that this effect was most robust when morphine was administered during first 2 h after ischemia (but not at 24 h). Previous studies have demonstrated an increased [^{3}H]naloxone binding in the striatum 1 h after transient cerebral ischemia in the gerbil.[28] This would suggest that a transient up-regulation of opioid receptors during the early period of reflow can represent a mechanism for the observed effect.

Whether the activation of opioid receptors plays a role in the development of irreversible neuronal degeneration after injurious intervals of brain and/or spinal ischemia is not clearly defined. Experimental studies showed that naloxone can ameliorate motor dysfunction after transient spinal cord ischemia in the rabbit.[29] However, subsequent experimental and clinical studies failed to demonstrate a significant beneficial effect of naloxone treatment on the neurologic outcome after acute stroke.[30–33]

An additional variable may reflect the time point when morphine is administered after spinal injury as well as the nature of spinal injury (*i.e.*, ischemic *vs.* traumatic). Thus, spinal morphine has been shown to produce a decrease in spasticity after chronic spinal *traumatic* injury in rats[34] and in humans.[13] Although the mechanism of this effect is not clear, it was reported that chronic traumatic spinal injury is associated with a selective loss of small inhibitory neurons.[35] Thus, the mechanism of morphine's spasticity-relieving effect observed after chronic spinal injury may reflect a hyperpolarization of persisting ventral α motoneurons.[2]

Conclusion

Neuraxial morphine administration during the early period of reflow after transient aortic occlusion may be associated with a transient motor dysfunction in humans undergoing thoracoabdominal aortic aneurysm resection and in rats subjected to a noninjurious interval of spinal ischemia. This effect is transient and can be reversed by naloxone. Histopathological analysis of the spinal cords of rats at 48 h after morphine treatment showed the occasional presence of dark-staining α motoneurons and interneurons. The implications that these may be markers of predegenerative neuronal injury that could be aggravated by the administration of opioids is a concern, although behaviorally, there was no evidence of a persistent neurologic dysfunction in the rats or human studied.

Appendix: Case Report

A 73-yr-old woman presented to the Massachusetts General Hospital (Boston, Massachusetts) with an enlarging 6.3-cm type III (Crawford classification) thoracoabdominal aneurysm, with an occluded right renal artery and stenotic superior mesenteric artery, for resection and repair. Her medical history was significant for long-standing hypertension and a previous inferior myocardial infarction. She had no recent history of angina and a good exercise capacity. A Persantine (The Du Pont Merck Pharmaceutical Co., Billerica, MA) thallium perfusion study showed no redistribution abnormalities, and cardiac echography showed overall preserved ventricular functional with inferior wall hypokinesis. Three years prior to admission, she underwent resection of a pituitary meningioma and placement of a ventriculoperitoneal shunt with an uneventful recovery and no remaining neurologic deficits. Her abdominal computed tomography scan revealed a dense and shrunken right kidney. Her baseline creatinine was 1.2. Her medications included hydrocortisone, 20 mg every morning and 10 mg every hour of sleep, and metoprolol, 50 mg every morning.

In the operating room, a 4-French epidural catheter at T11–T12 and a 4-French intrathecal single-lumen thermistor catheter at L3–L4 were placed for use with the epidural spinal cord cooling technique.[36,37] An 8.5-French antecubital intravenous catheter was used in conjunction with the Level One Rapid Infusion warming device, and an 18-gauge right radial arterial catheter was placed. A pulmonary artery catheter was inserted through the right internal jugular vein. Twelve milliliters lidocaine, 2%, with 1:200,000 epinephrine was given in divided doses through the epidural catheter, and a sensory block to T4 was demonstrated. General anesthesia was then induced with 150 μg fentanyl and 150 mg sodium thiopental and was maintained with 66% nitrous oxide–34% oxygen. A 37-French right-sided double-lumen endotracheal tube was placed. Relaxation was induced and maintained with atracurium. A hot air–warming blanket was used over the exposed upper thorax and head and arms. Epidural cooling was initiated with iced normal saline at 300 ml/h and titrated to maintain a cerebrospinal fluid temperature of 25°C. Blood pressure was supported as necessary prior to aortic cross clamping with a phenylephrine infusion. Mannitol, 25 g, was infused prior to aortic cross clamping. Using the clamp and sew technique, the aorta was clamped at the T8 level. Blood pressure was controlled with sodium nitroprusside to maintain a systolic pressure of 85–100 mmHg to facilitate completion of the proximal anastomosis.

With initial aortic cross clamping, large V waves were noted on the pulmonary artery tracing, and 4- to 5-mm ST segment depression were seen in leads I and V5 of the electrocardiogram. Heart rate was slowed with bolus doses of propranolol to 50/min, and increasing doses of nitroglycerin were infused while the sodium nitroprusside was weaned. Hemodynamics improved, though myocardial dysfunction did not resolve completely until the aortic clamp was moved to below the visceral anastomosis and the blood pressure was allowed to rise to

approximately 120/60 mmHg. The cross clamp times were 55 min for the proximal anastomosis and mesenteric vessels, 73 min for the left renal, and 104 min for the distal aortic and inferior mesenteric artery anastomoses. No further epidural lidocaine was administered after aortic cross clamping. Preservative-free morphine, 4 mg, was given through the epidural catheter upon cessation of epidural cooling after the distal anastomosis was completed. The remainder of the case proceeded uneventfully. Estimated blood loss was 3,800 ml. The patient received 1,500 ml crystalloid, 1,500 ml autotransfusion, 4 units of packed red blood cells, 2 l albumin (5%), 4 units of fresh frozen plasma, and 6 units of platelets. Epidural saline, 900 ml, was given during cooling. At the end of the case, 100 mg propofol was given, and the double-lumen endotracheal tube was replaced with a 7.5 single-lumen tube.

While still in the operating room, the patient was easily awakened and assessed neurologically. She was alert, awake and comfortable and followed commands but was unable to move her legs. She demonstrated good upper extremity grip strength bilaterally and was able to lift her head off the pillow easily. Sensory perception to light touch and fine point and temperature were intact in all extremities; patellar reflexes were absent; and a moderate amount of muscle tone was noted in her quadriceps. Her cerebrospinal fluid pressure was measured and found to be 12 mmHg, and 20 ml cerebrospinal fluid was withdrawn from the spinal catheter. Cerebrospinal fluid and body temperatures were 35°C. Her neurologic examination remained unchanged for the next 30 min. Upon arrival to the ICU, 40 μg naloxone was given intravenously. Within a few minutes, the patient commenced to move her legs and had complete return of lower extremity motor function and strength shortly thereafter. The remainder of her hospital stay was unremarkable, and she had no further neurologic events.

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