

Intrathecal Clonidine: Analgesia and Effect on Opiate Withdrawal in the Rat

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Clonidine, an α_2 adrenergic agonist, has analgesic properties and recently has been used to suppress opiate withdrawal. These two properties theoretically make it a suitable analgesic substitute in patients tolerant to opioids. The objectives of this study were to see if intrathecal clonidine is analgesic and whether it can modify morphine withdrawal at the spinal level. Rats chronically implanted with catheters in the lumbar subarachnoid space were utilized. In analgesia experiments, intrathecal clonidine produced analgesia with the peak effect in the paw-lick test occurring at 200 nm, and in the tail-flick test analgesia was apparent at 100 nm and peaked at 400 nm (in 10 μ L Ringer's lactate). In dependency experiments, animals dependent on morphine (300 mg \cdot kg $^{-1}$) received intrathecal clonidine 25, 50, 200 nm in 10 μ L Ringer's lactate 72 h after morphine. Following this, a naloxone challenge, 3 mg \cdot kg $^{-1}$ was administered and withdrawal assessed.

Clonidine-treated animals showed significant weight loss and decrease in temperature, and those treated with high doses showed marked hyperthermia and hind-limb flaccidity. Intrathecal clonidine prevented the hyperalgesia associated with opiate withdrawal but did not affect the occurrence of the majority of behavioral signs (e.g., piloerection, irritability) associated with morphine withdrawal. Intrathecal clonidine prevented the naloxone-induced increase in blood pressure during withdrawal and in animals not treated with morphine-produced hypotension. Thus, intrathecal clonidine is analgesic, and part of the antiwithdrawal action of clonidine may be exerted at the spinal level. (Key words: Analgesics: clonidine; morphine; tolerance. Anesthetic techniques: spinal. Antagonists, narcotic: naloxone. Spinal cord: receptors.)

CLONIDINE, an α_2 adrenergic receptor agent, used in the treatment of hypertension, is an agent of considerable interest to anesthetists. Systemic clonidine decreases MAC,¹ has analgesic properties,² and can give rise to an acute perioperative clonidine withdrawal syndrome.³ Animal studies show that the intrathecal injection of α -receptor agonists, including clonidine, produce analgesia that is comparable to analgesia produced by opioids.⁴ Recently, clonidine has become the drug of choice in suppressing withdrawal signs in individuals physically dependent on opioids.^{5,6} The ability of clonidine to induce analgesia via a distinct receptor and to suppress signs of opioid withdrawal theoretically

would make it a suitable substitute in patients who have become tolerant to the analgesic action of opioids but who must be maintained pain-free while avoiding the occurrence of withdrawal.

The ability of clonidine to suppress opiate withdrawal appears related to the inhibition of neurotransmission in the noradrenergic pathways arising from the locus coeruleus in the brain.⁷ However, in a recent study it was proposed that clonidine may act at the spinal cord level to suppress opiate withdrawal.⁸ This proposal is based on the observation that in the cat, systemically administered clonidine, like opioids, suppresses the electrical evoked activity in preganglionic neurons. Presently it is not known whether clonidine acts at the spinal level to suppress manifestations of opiate withdrawal. If this effect of clonidine could be demonstrated, this drug may become a potentially useful adjunct to spinal opioid analgesia. The objectives of our study were to determine whether spinally administered clonidine is analgesic and whether it can modify the physiologic and behavioral manifestations of opiate withdrawal.

Methods

All experiments were performed on male Sprague-Dawley rats (250–500 g).

ANALGESIC EXPERIMENTS

The analgesic action of clonidine was tested in rats chronically implanted with polyethylene catheters (PE10) in the lumbar subarachnoid space according to the technique of Yaksh and Rudy.⁹ Intrathecal clonidine, 100, 200, 300, or 400 nm in 10 μ L Ringer's lactate, was administered and analgesia assessed by the tail-flick¹⁰ and paw-lick (hot plate, temperature 52° C) tests.¹¹ The tail-flick test uses radiant heat from a projection lamp as a pain stimulus and the tail-flick as the end-point. In the paw-lick test the animals are placed on a heated aluminum plate of a thermal plate analgesia meter (Technilab Instruments, Pequannock, NJ) and the latency of the hind paw-lick recorded. Appropriate cut-off times were used to avoid thermal injury. Analgesia was assessed as the per cent maximal possible effect (%MPE).

$$\%MPE = \frac{\text{Postdrug latency} - \text{baseline (s)}}{\text{Cut off time} - \text{baseline (s)}} \times 100$$

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WITHDRAWAL EXPERIMENTS

The effect of intrathecal clonidine on morphine withdrawal was assessed in behavioral and cardiovascular experiments. Dependence on morphine was induced by the technique of Fredrickson and Smits.¹² A single injection of morphine suspension, 300 mg · kg⁻¹, was administered subcutaneously. Seventy-two hours after this injection, animals received either intrathecal clonidine 25, 50, 200 nM in 10 μl Ringer's lactate or 10 μl Ringer's lactate. Clonidine- or vehicle-treated animals were challenged with naloxone 3 mg · kg⁻¹ intraperitoneally (in blood pressure experiments—intravenously). The withdrawal syndrome precipitated by naloxone was assessed by observing temperature change, weight loss, and the presence of typical signs such as piloerection, defecation, vocalization, irritability, and hyperpnea. The number of animals exhibiting these signs in the control and clonidine-treated groups was noted.

In a group of animals the tail-flick response before and after naloxone challenge also was determined.

To assess clonidine's effect on the cardiovascular manifestations of morphine withdrawal, femoral artery blood pressure was recorded in vagotomized dependent rats anesthetized with chloralose. Ringer's lactate or clonidine in Ringer's lactate was administered intrathecally as described above, and changes in systolic blood pressure following naloxone administration were recorded.

Results were analyzed using the Student's *t* test and Chi-square test where appropriate and significance assessed at the *P* < 0.05 level.

Results

ANALGESIC EXPERIMENTS

Intrathecal administered clonidine produced analgesia in the tail-flick and paw-lick tests, as shown in figures 1 and 2. The peak effect in the paw-lick test occurred at 200 nM. In the tail-flick test clonidine analgesia became apparent at 100 nM and peaked at 400 nM.

WITHDRAWAL EXPERIMENTS

Table 1 shows the results of withdrawal on temperature and body weight. Animals dependent on morphine that had been pretreated with Ringer's lactate showed a significant increase in body temperature and a loss in body weight when challenged with naloxone. Clonidine-treated animals showed a decrease in temperature that was significant with the 50-nM dose and also experienced a significant weight loss during with-

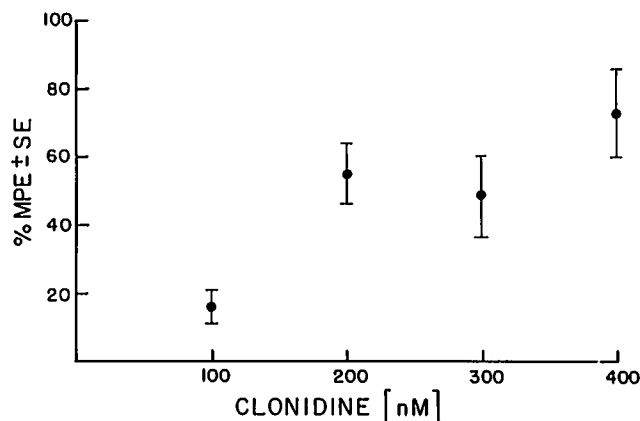


FIG. 1. Effect of intrathecal clonidine on paw-lick analgesia

$$\%MPE = \frac{\text{post drug latency} - \text{baseline (s)}}{\text{cut off time} - \text{baseline (s)}} \times 100.$$

drawal. At doses of 200 nM, intrathecal clonidine was associated with toxicity, producing marked hypothermia and in some animals hind-limb flaccidity.

Administration of naloxone to morphine dependent rats resulted in a significant decrease in tail-flick latency (fig. 3), an effect indicative of hyperalgesia. Animals treated with clonidine (25 and 50 nM) did not show a decline in tail-flick latency. Thus, in these tests, clonidine, used at doses considerably lower than those producing analgesia in naive animals, prevented the hyperalgesia associated with opiate withdrawal.

The effect of intrathecal clonidine treatment on the incidence of behavioral signs of morphine withdrawal are shown in table 2. As shown in the control group of dependent animals (Ringer's lactate injected), the signs elicited most frequently by naloxone were piloerec-

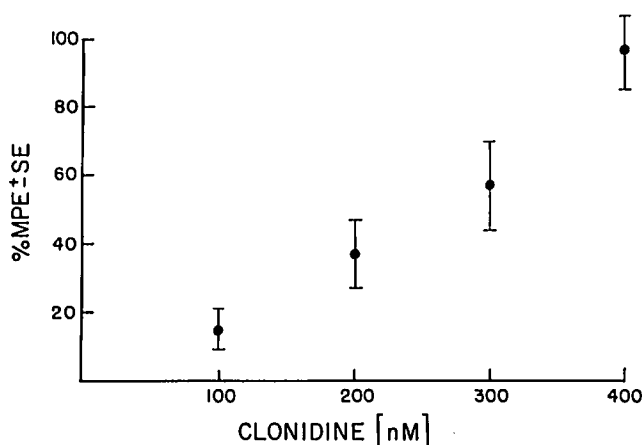


FIG. 2. Effect of intrathecal clonidine on tail-flick analgesia

$$\%MPE = \frac{\text{post drug latency} - \text{baseline (s)}}{\text{cut off time} - \text{baseline (s)}} \times 100.$$

TABLE 1. Temperature and Weight Loss after Naloxone Injection in Morphine-Treated Animals

Temperature	Ringer's Lactate (n = 14)	Clonidine 25 nM (n = 8)	Clonidine 50 nM (n = 10)
°C	37.49—*— 37.80	37.30—*— 36.93	37.20—*— 36.60
±SE	0.20 0.29	0.18 0.31	0.10 0.15
Weight loss			
Grams	260.4 —*—246.8	262.4 —*—249.0	369.8 —*—359.0
±SE	8.3 7.2	6.5 5.7	37.0 37.2

* $P < 0.05$ (Student's *t*).

tion, defecation, vocalization, irritability to light touch on stroking, and hyperpnea. While piloerection, vocalization, and defecation were not affected to a great extent by intrathecal clonidine, hyperpnea was reduced significantly.

The cardiovascular manifestations of naloxone induced morphine withdrawal are shown in figure 4. In morphine-dependent animals, administration of naloxone produced an immediate increase in blood pressure (fig. 4, upper trace). When these animals were treated with intrathecal clonidine prior to naloxone challenge, there was a significant decrease in systolic

blood pressure from 135 ± 9.5 (SE) mmHg to 95 ± 12.5 mmHg (Student's *t* test $P < 0.05$, $n = 5$). Administration of naloxone following clonidine pretreatment restored the blood pressure in these animals to control levels. Thus, in this group of animals pretreatment with clonidine prevented the naloxone-induced increase in blood pressure over original baseline values. In the group of animals receiving intrathecal Ringer's lactate, the injection did not affect the baseline blood pressure values but prevented the naloxone-induced increase in blood pressure that had been observed in animals not receiving intrathecal injections.

In naive chloralose anaesthetized rats, intrathecal clonidine (50 nM) produced a significant decrease in systolic blood pressure from 79 ± 10.2 (SE) to 61 ± 7.5 mmHg, while intravenous clonidine produced significant hypertension from 86 ± 6.59 (SE) to 158 ± 12.5 mmHg ($P < 0.05$, Student's *t* test, $n = 5$).

Discussion

In previous studies, Yaksh *et al.*^{4,13} have shown that spinal adrenergic neurons are involved in processing of nociceptive sensory information. Activation of adrenergic receptors in the spinal cord produces analgesia. Our study confirms the observations of Yaksh *et al.* that

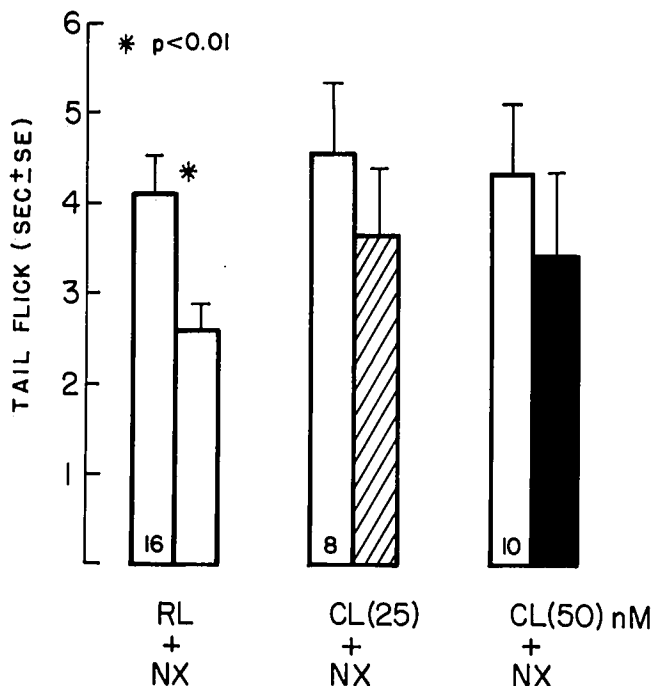


FIG. 3. Effect of intrathecal clonidine on morphine withdrawal hyperalgesia. The second column in each of the three pairs represents the response following naloxone. RL = Ringer's lactate; CL = clonidine; NX = naloxone. *n* values shown in bars. * $P < 0.01$, Student's *t*.

TABLE 2. Withdrawal Signs after Naloxone Injection in Morphine-Treated Animals (numbers represent % of animals demonstrating the indicated sign)

	Ringer's Lactate (n = 16)	Clonidine 25 nM (n = 8)	Clonidine 50 nM (n = 10)	
Piloerection	94	100	90	$P > 0.05$
Defecation	94	63	90	$P > 0.05$
Vocalization	63	63	60	$P > 0.05$
Irritability	63	13	40	$P > 0.05$
Hyperpnea	56	25	0	$P < 0.05^*$

* $P < .05$ (significance—Chi-square test).

intrathecal clonidine produces analgesia. Although a dose-response relationship for the analgesic action of clonidine is demonstrable, this action is associated with some toxicity, including hind limb flaccidity, hypothermia, and hypotension at high doses. The hypertension seen after intravenous administration of clonidine may be due to its action on peripheral alpha receptors. The difference in cardiovascular response between intrathecal and intravenous clonidine shows that the principal sites of action of the drug given by the two routes are different. A significant amount of intrathecal clonidine probably is not absorbed into the systemic circulation. However, the ability of clonidine to produce analgesia at lower doses, without producing toxicity, suggests that clonidine or other agents that activate α_2 receptors may have potential as intrathecal analgesics or as adjuncts to opioid analgesia. Substitution of clonidine for an opiate drug, thus providing an "opiate holiday," would allow opiate receptors that have become tolerant following prolonged exposure to such a drug to regain their sensitivity. Alternatively, a combination of a low dose of morphine and clonidine, resulting in a synergistic action, may produce analgesia but avoid the side effects of both agents, including the development of tolerance to morphine or clonidine. However, side effects of clonidine will have to be evaluated fully before clonidine can be used as an analgesic in humans. It would be of interest to determine whether side effects such as hind limb weakness, hypotension, and hypothermia can be dissociated from analgesia using other α_2 receptor agonists.

Opiate withdrawal associated with hyperalgesia is a well-known problem. This problem also may be anticipated in patients who are withdrawn from intrathecally administered opioids, since this has been demonstrated in animal studies.¹⁴ Intrathecal clonidine theoretically may be useful in suppressing this withdrawal while maintaining adequate analgesia. The action of intrathecal clonidine therefore was tested on morphine withdrawal in animals given continuous exposure to the systemic opioid for three days. In these experiments, intrathecal clonidine produced only a modest suppression of opioid withdrawal signs. The hyperalgesia and hyperpnea associated with withdrawal were the signs most affected by clonidine. Various other signs were not suppressed consistently by clonidine. The failure of clonidine to suppress withdrawal more completely may be due to two factors. First, systemic morphine was used to induce dependence and the withdrawal syndrome precipitated by naloxone may originate at central or peripheral sites not accessible to spinal clonidine. Greater success with clonidine might be

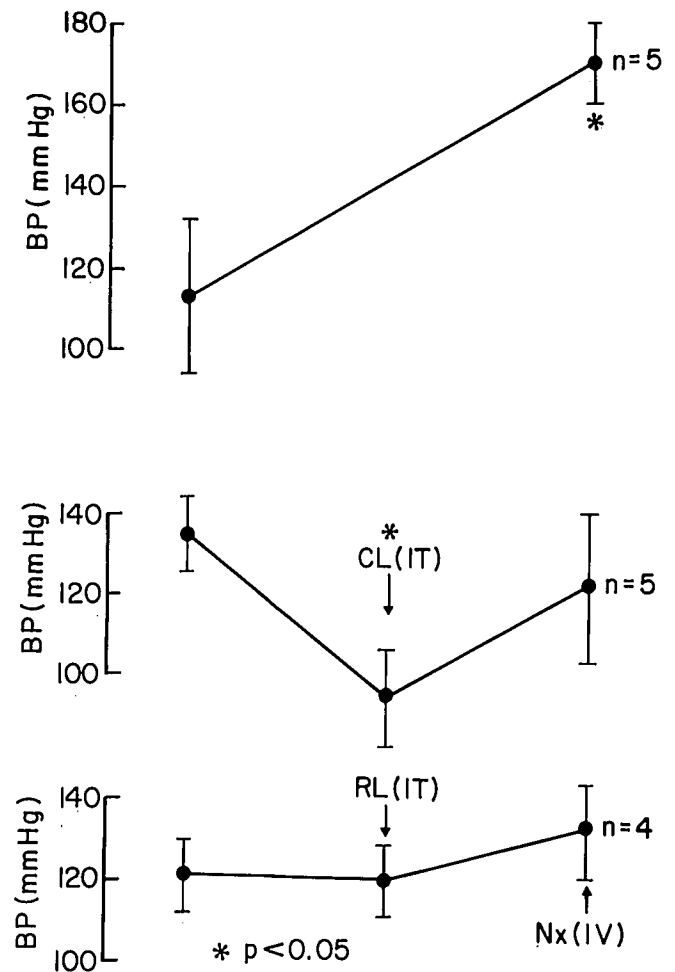


FIG. 4. Effect of intrathecal clonidine on systolic arterial blood pressure. Clonidine (CL) and Ringer's lactate (RL) were administered intrathecally (IT) followed by intravenous naloxone (Nx).

achieved in experiments where its action is tested on withdrawal from spinally administered opioids. Second, the doses of clonidine used were lower than those effective in analgesic tests. The doses used here have been kept low to avoid the toxicity that may result from higher doses. Since intrathecal clonidine does not suppress opioid withdrawal fully, it would appear that neurons in the spinal cord are not the principal sites of its action. However, part of the antiwithdrawal action of clonidine may be exerted at the spinal level.

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