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Study of Three Different Doses of Epidural Neostigmine Coadministered with Lidocaine for Postoperative Analgesia

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Background: **Intrathecal neostigmine produces analgesia in volunteers and patients. However, the use of epidural neostigmine has not been investigated. The purpose of the current study was to define the analgesic effectiveness of epidural neostigmine coadministered with lidocaine and side effects in patients after minor orthopedic procedures.**

Methods: **After Institutional Review Board approval and informed consent, 48 patients (n = 12) undergoing knee surgery were randomly allocated to one of four groups and studied in a prospective way. After 0.05–0.1 mg/kg intravenous midazolam premedication, patients were randomized to receive 20 mg intrathecal bupivacaine plus epidural lidocaine (85 mg) with saline (control group); 1 μg/kg epidural neostigmine (1 μg group); 2 μg/kg epidural neostigmine (2 μg group); or 4 μg/kg epidural neostigmine (4 μg group). The concept of the visual analog scale, which consisted of a 10-cm line with 0 equaling "no pain at all" and 10 equaling "the worst possible pain" was introduced. Postoperatively, pain was assessed using the visual analog scale, and intramuscular 75 mg diclofenac was available at patient request.**

Results: **Groups were demographically the same and did not differ in intraoperative characteristics (blood pressure, heart rate, ephedrine consumption, oxyhemoglobin saturation, sensory loss before start of surgery, or duration of sensory motor block). The visual analog scale score at first rescue analgesic and the incidence of adverse effects were similar among groups ($P > 0.05$). The time (min ± SD) to first rescue analgesic was as follows: control group: 205 ± 48; 1-μg group: 529 ± 314; 2-μg group: 504 ± 284; 4-μg group: 547 ± 263 ($P < 0.05$). The analgesic consumption (number of intramuscular diclofenac injections [mean, 25th–75th percentile]) in 24 h was as follows: control group: 3 [3 or 4]; 1-μg group: 1 [1 or 2]; 2-μg group: 2 [1 or 2]; 4-μg group: 2 [1–3] ($P < 0.05$). The 24-h-pain visual analog scale score (cm ± SD) that represents the overall impression for the last 24 h was as follows: control group: 5 ± 1.6; 1-μg group: 1.6 ± 1.8; 2-μg group: 1.4 ± 1.6; 4-μg group: 2.2 ± 1.9 ($P < 0.005$). The incidence of adverse effects was similar among groups ($P > 0.05$).**

Conclusion: **Epidural neostigmine (1, 2, or 4 μg/kg) in lidocaine produced a dose-independent analgesic effect (≈ 8 h) compared to the control group (≈ 3.5 h), and a reduction in postoperative rescue analgesic consumption without increasing the incidence of adverse effects. (Key words: Arthroscopy; cholinergic; pain relief.)**

INTRATHECAL injection of neostigmine increases concentrations of acetylcholine in the cerebrospinal fluid and produces analgesia in animals[1–3], which is blocked by the intrathecal administration of muscarinic antagonists.[1–3] Intrathecal neostigmine also produces analgesia in humans with acute experimental and postoperative pain.[4–8] In a series of clinical studies, intrathecal neostigmine doses, ranging from 25 μg to 100 μg caused a dose-independent analgesic effect and a dose-related incidence of adverse effects in patients undergoing vaginal hysterectomy[7] and orthopedic surgery,[8] with nausea and vomiting being the most troublesome during the intrathecal anesthetic technique. Further study of patients suggested that intrathecal neostigmine doses as low as 5 μg[9] or 10 μg[10] still had analgesic properties, with no or a very low incidence of side effects.

The analgesia and side effects of epidural neostigmine have not been investigated. This study was conducted to evaluate analgesia and side effects of epidural neostigmine coadministered with lidocaine in orthopedic procedures.

Materials and Methods

The Ethical Committee of the University of São Paulo Teaching Hospital, Ribeirão Preto approved the study protocol. After giving informed consent, 48 patients, American

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Society of Anesthesiologists status I and II, scheduled for minor orthopedic procedures were randomized to one of four groups (n = 12 each) and prospectively studied using a placebo-controlled double-blind design to evaluate analgesia and adverse effects. The concept of visual analog scale (VAS), which consisted of a 10-cm line with 0 equaling "no pain at all" or "no nausea" (VAS N); and 10 equaling "the worst possible pain" or "worst possible nausea" was introduced before surgery.

Patients were premedicated with intravenous midazolam, 0.05–0.1 mg/kg, in the holding room. Hydration consisted of 10 ml/kg lactate solution preoperatively and 10 $ml \cdot kg^{-1} \cdot h^{-1}$ after spinal anesthesia. The randomization was computer generated. The epidural spinal injection using the loss-of-resistance-to-air technique and a 17-gauge needle was performed in the operating room at the L3–L4 or L2–L3 interspaces with the patient in the sitting position. The control group received saline as the epidural test drug diluted with lidocaine. The 1-μg group received 1 μg/kg epidural neostigmine as the test drug. The 2-μg group received 2 μg/kg epidural neostigmine as the test drug; and the 4-μg group received 4 μg/kg epidural neostigmine. The neostigmine was diluted to a concentration of 50-μg/ml for the 1-μg group; to 100 μg/ml for the 2-μg group; and to 200 μg/ml for the 4-μg group. This test solution was prepared by one anesthesiologist. The second anesthesiologist who was blinded to the preparation diluted the test solution to a final 10-ml volume with 1% lidocaine (approximately 85 mg lidocaine in the final preparation for all groups). The epidural test drug (saline or neostigmine) in lidocaine was injected slowly ($\approx$ 2 min) after a 3-ml test dose. Immediately after the epidural injection, 20 mg hyperbaric bupivacaine (4 ml) was injected at the rate of 1 ml/7 s through a 25- or 27-gauge intrathecal needle in the interspace bellow. Patients were placed in the supine position after spinal injection.

Intraoperative sensory loss was assessed by pin prick at 5 and 10 min after the injection. Blood pressure was monitored noninvasively every 5 min throughout surgery, and heart rate and oxyhemoglobin saturation (Sp_{O_2}) were continuously monitored throughout surgery. A decrease in mean arterial pressure greater than 15% below preanesthetic baseline was treated by incremental doses of ephedrine, 4 mg intravenously. Decreases in heart rate less than 50 beats/min were treated with incremental doses of atropine, 0.25 mg intravenously. The patient using the 10-cm VAS N scored nausea. The number of patients having nausea (of any degree) or vomiting at any point intraoperatively was noted. Nausea greater than 2/10 (measured by the VAS pain score) or vomiting were treated with 20 mg intravenous metoclopramide followed by 0.5 mg intravenous droperidol, if necessary.

Postoperative assessment included pain scores at fixed intervals (3, 6, 9, 12, 24 h) and adverse effects and the duration of motor block, measured from anesthetic injection until the time to reach Bromage 2 score.[11] Postoperative nausea and occurrence of vomiting were assessed postoperatively at fixed intervals. Metoclopramide, 20 mg intravenously, followed by droperidol, 0.5 mg intravenously, if necessary, were administered when VAS N was more than 2 cm or during occurrence of vomiting. Duration of effective analgesia was measured as time from the spinal drug administration to the patient's first request for analgesic administration in the recovery room, recorded in minutes. The VAS at the time of first rescue analgesic medication was measured using the 10-cm VAS. Intramuscular diclofenac, 75 mg, was available if requested by the patient. The 24-h VAS pain score and VAS N reflected the patient's overall impression of the 24 h after spinal injection.

Statistical Analysis

The number of subjects per group (n = 12) was based on previous preliminary experience. We hypothesized that epidural 4μg/kg neostigmine would increase the time to first rescue analgesic by 100% when compared to control group. If we estimated a standard deviation for this prospective power analysis at 40% and an α value of 0.05, these assumptions would require five patients in each group to see a 100% increase in the time the first rescue analgesic. To further increase the power we elected to observe 12 patients in each group. Groups were compared for demographic data (age, weight, and height) by one-way analysis of variance. Incidence of adverse events, gender, and site of primary disease were compared among groups by chi-square analysis corrected for multiple tests ($P < 0.05$ or 0.0125). The time to first rescue analgesics was compared among groups by one-way analysis of variance. VAS scores were compared among groups by two-way analysis of variance for repeated measures.[12] Tukey Honest analysis was applied to correct P values. $P < 0.05$ was considered significant.

Results

The four groups did not differ with respect to gender, American Society Anesthesiologists status, weight, age, and height. The distribution of the types of surgical procedures was similar among groups (table 1). The

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Table 1. Demographic Analysis

Group	Gender (male/female)	ASA Status (I/II)	Weight (kg)*	Age (yr)*	Height (cm)*	Type of Surgery (knee arthroplasty/arthroscopy, meniscus repair)
Control	5/7	9/3	62 ± 12	31 ± 19	164 ± 16	3/9
1 μg/kg neostigmine	5/7	8/4	66 ± 15	34 ± 16	161 ± 10	3/9
2 μg/kg neostigmine	5/7	8/4	66 ± 13	35 ± 19	165 ± 11	3/9
4 μg/kg neostigmine	6/6	8/4	67 ± 18	34 ± 15	160 ± 14	2/10
P	0.9999	0.9999	0.9139	0.955	0.8261	0.9044

* Data are mean ± SD.

surgical time, anesthetic time, level to pin prick at 5 and 10 min, and intraoperative ephedrine consumption were also similar among groups (table 2). The mean blood pressure and heart rate at regular intervals after the spinal injection were also the same in all groups.

The postoperative pain data are described in table 3. The VAS score at first rescue analgesic was the same among groups. The time (min) to first rescue analgesic was greater for all three neostigmine groups (500–547 min) *versus* the control group (205 ± 48 min) ($P < 0.05$). The number of intramuscular diclofenac injections ([median, 25th–75th percentile]) during the first 24 h postoperatively was less for the 1-μg group, (1 [1 or 2]); 2-μg group (2 [1 or 2]); and the 4-μg group (2 [1–3]), all compared to the control group (3 [3 or 4]) ($P < 0.05$). The 24-h-pain VAS score that meant the overall impression for the 24 h after the spinal punction was also less for the 1-μg group (1.6 ± 1.8), 2-μg group (1.4 ± 1.6), and the 4-μg group (2.2 ± 1.9), all compared to the control group (5 ± 1.6) ($P < 0.005$). Figure 1 displays the VAS pain scores for the groups at fixed intervals.

There were no differences regarding the incidence of perioperative adverse effects. Intraoperatively, none of the patients complained of nausea or vomiting. One patient from the 1-μg group and one from the 4-μg group had bradycardia 40 and 180 min, respectively, after the spinal injection and were treated with intravenous atropine. Postoperatively, two patients from the control group (VAS N = 2 and 10 cm), three patients from the 1-μg group (VAS N = 2, 4, and 5 cm), two patients from the 2-μg group (VAS N = 3 and 7 cm), and one patient from the 4-μg group (VAS N = 10 cm) complained of nausea or occurrence of vomiting during breakfast the next morning. The 24-h-nausea VAS scores that meant the overall impression for the last 24 h since the spinal puncture (mean ± SD, cm) were as follows: control group (1 ± 3) = 1-μg group (1 ± 2) = 2 μg group (1 ± 2) = 4-μg group (1 ± 3) ($P = 0.9402$).

Discussion

This clinical research has shown a dose-independent analgesic effect of 1, 2, and 4 μg/kg epidural neostigmine combined with ≈ 85 mg lidocaine in minor orthopedic procedures, compared with lidocaine in saline. This was reflected by the time to first rescue analgesic (8 h compared to 3.5 h for the control group) and rescue analgesic consumption during the first 24 h postoperatively.

We hypothesized that the analgesia mediated by epidural neostigmine is caused by the drug spread into the cerebrospinal fluid at approximately 1/10 of the initial epidural dose administered. Neostigmine is a hydrophilic molecule, similar to morphine. Only 10–20% of an extradural dose of morphine crosses the dura mater into the cerebrospinal fluid. This is reflected in the higher doses used by this route: 10 mg extradural morphine daily is equivalent to 1 mg daily intrathecal morphine.[13] The translation of these data to the use of epidural

Table 2. Intraoperative Data

	Control	1 μg/kg Neostigmine	2 μg/kg Neostigmine	4 μg/kg Neostigmine	*P*
Surgical time (min)	123 ± 19	109 ± 32	125 ± 45	125 ± 25	0.7265
Anesthetic time (min)	177 ± 36	156 ± 19	172 ± 24	194 ± 48	0.1291
Level to pinprick at 5 min	8 ± 2	8 ± 2	7 ± 2	8 ± 2	0.6399
Level to pinprick at 10 min	6 ± 2	6 ± 1	5 ± 1	6 ± 2	0.3446
Ephedrine consumption	2.3 ± 3	3 ± 4.6	2.3 ± 4.3	2.2 ± 4.3	0.9720

Data are mean ± SD.

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Table 3. Postoperative Pain Data

	Control	1 μg/kg Neostigmine	2 μg/kg Neostigmine	4 μg/kg Neostigmine
Time for first rescue analgesic (min)*	205 ± 48	529 ± 314	504 ± 284	547 ± 263
VAS score at first rescue analgesic†	7 ± 2	6 ± 2	7 ± 1	6 ± 2
Number of intramuscular diclofenac injections in 24 h‡	3 (3–4)	1 (1–2)	2 (1–2)	2 (1–3)
VAS 24 h§	5 ± 1.6	1.6 ± 1.8	1.4 ± 1.6	2.2 ± 1.9

Number of intramuscular diclofenac injections are expressed as median (25th–75th percentile). Other data are mean ± SD.

* Control group differs from 1, 2, and 4 μg groups; control group *versus* 1 μg group ($P = 0.023045$); control group *versus* 2 μg group ($P = 0.023450$); control group *versus* 4 μg group ($P = 0.011746$).

† $P = 0.7641$.

‡ Control group differs from 1, 2, and 4 μg groups; control group *versus* 1 μg group ($P = 0.003848$); control group *versus* 2 μg group ($P = 0.001226$); control group *versus* 4 μg group ($P = 0.028562$).

§ Control group differs from 1, 2, and 4 μg groups; control group *versus* 1 μg group ($P = 0.00454$); control group *versus* 2 μg group ($P = 0.000303$); control group *versus* 4 μg group ($P = 0.004211$).

neostigmine obeyed a simplistic thought: to determine a dose with which to start. As previously described, the literature suggests that low intrathecal neostigmine doses, such as 5[9] or 10 μg[10] can be effective as part of multimodal analgesia for pain relief. The administration *via* epidural of ten times the lowest known effective intrathecal neostigmine dose (5–10 μg), could show some analgesic effect for treating postoperative pain. Consequently, intrathecal 10 μg would be somewhat related to 100 μg epidural neostigmine (or 2 μg/kg for an average 50-kg patient), and 5 μg intrathecal neostigmine would be related to 1 μg/kg epidurally. Spinally administered drugs reach their sites of action by diffusion into the spinal cord and roots, and the effects of a highly polar compound, such as neostigmine, may differ depending on the depth of tissue it must penetrate to act. However, the possibility of a dural puncture enhancing the movement of the epidurally administered neostigmine into the subarachnoid space, as it has been shown in sheep, after the spinal administration of sufentanil[14] cannot be excluded. Intrathecal neostigmine produces analgesia in animals[1–3], volunteers,[4] and patients[5–8,10] as a result of inhibiting the breakdown of the central neurotransmittor acetylcholine. Spinal muscarinic (M1 in sheep) receptors are believed to be involved in the analgesic properties of spinal neostigmine.[1,2] Autoradiographic studies have shown muscarinic binding in the substantia gelatinosa and, to a lesser extent, in the laminae III and V of the dorsal gray of the spinal cord,[15] coincident with opioid and adrenergic sites. Moreover, the analgesia mediated by spinal α_2-adrenergic agonists is in part mediated by cholinergic activation.[16]

Whether the same neostigmine doses used (1, 2, or 4 μg/kg) without local anesthetic would alter the analgesic profile is unknown and deserves further elucidation. It is possible that the small dose of epidural lidocaine has potentiated the neostigmine analgesic effect, and additive neostigmine doses would be ineffective. In addition, the lack of a dose-response for analgesia suggests that doses less than 1 μg/kg neostigmine should be tested before defining the ideal epidural dose. In a separate "part II" section of this study, five other patients were blinded study to compare 0.5 μg/kg epidural neostigmine in saline and 1 μg/kg epidural neostigmine in

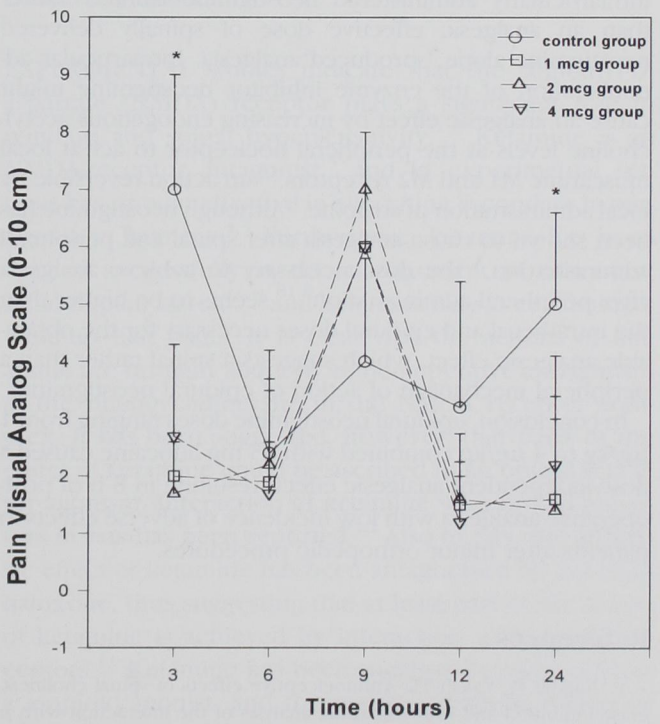

Fig. 1. Mean visual analog scores for postoperative pain at fixed intervals. Data are expressed as the mean ± SD. *P* values comparing visual analog scores at the same time range. 1-μg group − 1-μg/kg neostigmine group; 2-μg group − 2-μg/kg neostigmine group; 4-μg group − 4-μg/kg neostigmine group. * $P < 0.05$ (analysis of variancefor repeated measures, Tukey Honest analysis).

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saline. By the results of these five patients, we could see that, although 1 μg/kg neostigmine with lidocaine gave 8 h of postoperative analgesia (original work), 1 μg/kg neostigmine without lidocaine gave approximately 6 h of analgesia. The 0.5-μg/kg neostigmine group displayed 4 h of postoperative analgesia. The data from part II of the study suggests that going below 1 μg/kg epidural neostigmine may be inadvisable; however, the small number of patients is a limitation. A second possibility is that the lowest neostigmine dose (1 μg/kg) maximally potentiated the analgesic effect of lidocaine. During spinal and epidural anesthesia, the neurons of the dorsal horn are exposed to local anesthetics, which, in relevant concentrations, will block Na^+ and K_A currents but not delayed-rectifier K^+ currents in spinal dorsal horn neurons.[17] Nevertheless, this would require a dose–response study of epidural neostigmine alone for elucidation.

In addition to the spinal mechanism of action, neostigmine displays peripheral[1,18] and supraspinal[19] analgesic activity. The analgesic action of systemic anticholinesterase drugs such as physostigmine is believed to be a result of indirect stimulation of spinal muscarinic M1 receptors and supraspinal muscarinic M1 and M2 and nicotinic cholinergic receptors.[20,21] Peripherally, a tenfold higher dose of intraarticularly administered neostigmine alone,[18] rather than an analgesic effective dose of spinally delivered neostigmine alone,[5] produced analgesia. Intraarticular administration of the enzyme inhibitor neostigmine might cause an analgesic effect by increasing endogenous acetylcholine levels at the peripheral nociceptor to act at local muscarinic M1 and M2 receptors,[18] an action reversible by local administration of atropine.[1] Although neostigmine has been shown to cause analgesia after spinal and peripheral administration,[3] the dose necessary to achieve analgesia after peripheral administration[3,18] seems to be higher than the intrathecal and epidural doses necessary for the obtainable analgesic effect, which suggests a spinal rather than a peripheral mechanism of action of epidural neostigmine.

In conclusion, epidural neostigmine doses ranging from 1 μg/kg to 4 μg/kg combined with 85 mg lidocaine caused a dose-independent analgesic effect, resulting in 8 h of postoperative analgesia with low incidence of adverse effects in patients after minor orthopedic procedures.

References

1. Naguib M, Yaksh TL: Antinociceptive effects of spinal cholinesterase inhibition and isobolographic analysis of the interaction with μ and α2 receptor systems. ANESTHESIOLOGY 1994; 80:1338–48

2. Bouaziz H, Tong C, Eisenach JC: Postoperative analgesia from intrathecal neostigmine in sheep. Anesth Analg 1995; 80:1–5

3. Buerkle H, Boschin M, Marcus MAE, Brodner G, Wüsten R, Van Aken H: Central and peripheral analgesia mediated by the acetylcholisterase-inhibitor neostigmine in the rat inflamed knee joint model. Anesth Analg 1998; 86:1027–32

4. Hood DD, Eisenach JC, Tuttle R: Phase I safety assessment of intrathecal neostigmine in humans. ANESTHESIOLOGY 1995; 82:331–43

5. Lauretti GR, Reis MP, Prado WA, Klamt JG: Intrathecal morphine and neostigmine: Effective combined analgesic for postoperative pain in patients undergoing anterior and posterior vaginoplasty. Anesth Analg 1996; 82:1182–7

6. Pan PM, Huang CT, Wei TT, Mok MS: Enhancement of analgesic effect of intrathecal neostigmine and clonidine on bupivacaine spinal anesthesia. Reg Anesth 1998; 23:49–56

7. Lauretti GR, Hood DD, Eisenach JC, Pfeifer BL: A multicenter study of intrathecal neostigmine for analgesia following vaginal hysterectomy. ANESTHESIOLOGY 1998; 89:913–8

8. Lauretti GR, Mattos AL, Reis MP, Prado WA: Intrathecal neostigmine for postoperative analgesia after orthopedic surgery. J Clin Anesth 1997; 9:473–7

9. Lauretti GR, Oliveira APM, Reis MP, Mattos AL:. Transdermal nitroglycerine enhances spinal neostigmine postoperative analgesia following gynecological surgery(abstract). ANESTHESIOLOGY 1998; 89(3):1073A.

10. Kruskowski JA, Hood DD, Eisenach JC, Mallak KA, Parker RL: Intrathecal neostigmine for post cesarean section analgesia: Dose response. Anesth Analg 1997; 84:1269–75

11. Bromage PR. A comparison of the hydrochloride salts of lidocaine and prilocaine in epidural analgesia. Acta Anesthesiol Scand 1965; 16:55–9

12. Dexter F, Chestnut DH: Analysis of statistical tests to compare visual analog scale measurements among groups. ANESTHESIOLOGY 1995; 82:896–902

13. Watson PJQ, Moore RA, McQuay HJ: Plasma morphine concentration and analgesic effects of lumbar extradural morphine and heroin. Anesth Analg 1984; 63:629–34

14. Swenson JD, Lee TS, M-James S: The effect of prior dural puncture on cerebrospinal fluid sufentanil concentrations in sheep after the administration of epidural sufentanil. Anesth Analg 1998; 86:794–6

15. Wamsley JK, Lewis MS, Young WS III, Kuhar MJ: Autoradiographic localisation of muscarinic cholinergic receptors in rat brainstem. J Neurosci 1981; 1:176–91

16. Klimscha W, Tong C, Eisenach JC: Intrathecal α2-adrenergic agonists stimulate acetylcholine and norepinephrine release from the spinal cord dorsal horn in sheep. ANESTHESIOLOGY 1997; 87:110–6

17. Olschewski A, Hempelmann G, Vogel W, Safronov BV: Blockade of Na+ and K+ currents by local anesthetics in the dorsal horn neurons of the spinal cord. ANESTHESIOLOGY 1998; 88:172–9

18. Yang LC, Chen LM, Wang CJ, Buerkle H. Postoperative analgesia by intraarticular neostigmine in patients undergoing knee arthroscopy. ANESTHESIOLOGY 1998; 88:334–9

19. Beilin B, Nemirovisky AY, Zeidel A, Maibord E, Zelman V, Katz RL: Systemic physostigmine increases the antinociceptive effect of spinal morphine. Pain 1997; 70:217–21

20. Pan ZZ, Williams JT: Muscarine hyperpolarizes a subpopulation of neurons by activating an M2 muscarinic rceptor in rat nucleos raphe magnus in vitro. J Neurosci 1994; 14(3):1332–8

21. Iwamoto ET: Characterization of the antinociception induced by nicotine in the tegmental nucleus and the nucleus raphe magnus. J Pharmacol Exp Ther 1991; 257:120–33

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