Intrathecal Adenosine

Interactions with Spinal Clonidine and Neostigmine in Rat Models of Acute Nociception and Postoperative Hypersensitivity

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Background: Spinal adenosine receptor agonists exert antinociceptive effects in animal models of acute and chronic pain, but adenosine itself has not been examined. The authors tested the antinociceptive and antihypersensitivity interactions of intrathecal adenosine and its interactions with intrathecal clonidine and neostigmine in rat models of acute thermal nociception and postoperative hypersensitivity.

Methods: Rats were prepared with lumbar intrathecal catheters. Responses to acute noxious stimulation were evaluated by latency to paw withdrawal from a radiant heat source focused on the hind paw. Postoperative hypersensitivity was measured after an incision in the rat hind paw by application of von Frey filaments to the heel adjacent to the wound. An isobolographic design was used to distinguish between additive and synergistic drug interactions.

Results: Spinal administration of clonidine and neostigmine, but not adenosine, produced dose-dependent antinociception to noxious thermal stimulation. Addition of adenosine enhanced the antinociceptive effect of clonidine but not neostigmine in contrast, each of these three agents alone reversed postoperative hypersensitivity. Pretreatment with the α-adrenergic antagonist phentolamine completely reversed adenosine's antihypersensitivity action. Adenosine interacted synergistically with neostigmine and additively with clonidine in reducing postoperative hypersensitivity.

Conclusions: These data indicate that intrathecal adenosine by itself has no antinociceptive properties to acute noxious thermal stimulation in rats, but enhances clonidine's antinociception. In contrast, intrathecal adenosine is active against postoperative hypersensitivity by an adrenergic mechanism.

Different interactions between adenosine, clonidine, and neostigmine in acute nociception and postoperative hypersensitivity models are consistent with altered central processing of sensory information after peripheral injury. (Key words: Adrenergic; alldynia; postoperative pain; purinergic.)

INCREASED understanding of endogenous pain modulatory systems that alter nociceptive transmission in the spinal cord of animals and humans has led to the development of receptor-specific agents (opioids, α₂-adrenergic agonists, cholinesterase inhibitors) in humans. Adenosine has also been recognized to play a role in modulation of nociceptive information at the spinal level.1 Adenosine receptors are present in the substantia gelatiosa, where primary afferent neurons transmitting noxious information terminate.2 Both A1 and A2 subtypes of adenosine receptors have been identified in the substantia gelatiosa on intrinsic neurons.3 Intrathecal administration of adenosine receptor agonists produces antinociception in animals.1,4 In addition, adenosine agonists synergistically enhance antinociception from noradrenaline and α₂-adrenergic agonists5,6 in a rat model of acute thermal nociception. α₂-Adrenergic agonists produce antinociception in part by activation of spinal cholinergic interneurons,7,8 and intrathecally applied cholinomimetic drugs and cholinesterase inhibitors produce dose-dependent antinociception in rats and cats.9,10 This finding implies that spinal adenosine receptor stimulation might synergistically enhance antinociception from spinal cholinergic agents. One purpose of the current study was to test this hypothesis.

Postoperative pain has commonly been considered a form of acute pain, but pain from a surgical incision also induces mechanical hyperalgesia surrounding the wound in patients.11 Recently a rat model of incisional pain has been developed that demonstrates reproducible, quantifiable mechanical allodynia lasting for several days after the incision.12 It has been suggested that this model displays similarities to the human postoperative

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pain state. Mechanical hypersensitivity evoked by nerve injury can be powerfully reversed by α₂-adrenergic agonists and neostigmine. Although intrathecal adenosine receptor agonists have been shown to reduce hypersensitivity in rat models of ligation of the 5th and 6th lumbar spinal nerve, inflammatory hyperalgesia, and chronic central pain, they have not been examined in this postoperative model. A second purpose of the current study was to test the efficacy of intrathecal adenosine in this model.

All previous studies have been conducted with synthetic adenosine receptor agonists rather than with adenosine itself. Because adenosine is commercially available in a preservative-free solution in the United States and has undergone neurotoxicity testing in Sweden where it is being examined in humans, the effects of adenosine itself in these models of pain are clinically relevant. We therefore investigated the antinociceptive properties of intrathecal adenosine itself, in the US commercially available preparation, to an acute noxious thermal stimulus and on mechanical hypersensitivity after a surgical incision. Interactions between adenosine and clonidine and neostigmine were assessed in both models.

**Methods**

**Animals**

Studies were approved by the Animal Care and Use Committee, Wake Forest University School of Medicine. Sixty-six male Sprague-Dawley rats (Harlan, Indianapolis, IN), weighing 250–300 g, were studied. A lumbar intrathecal catheter was inserted during general anesthesia with halothane via an incision in the atlantooccipital membrane, as previously described. The intrathecal catheter was passed 8 cm caudally to the level of the lumbar enlargement. The end of the catheter was externalized on top of the skull and closed by melting. Before implantation, the catheter was prepared in the following way: PE 5 (polyethylene, ID 0.008 inch, OD 0.014 inch, Spectra, Colorado Springs, CO) tubing was connected with PE 10 (polyethylene, ID 0.011 inch, OD 0.024 inch, Becton-Dickinson, Sparks, MD) tubing over a metal wire using a heat gun, so that the length of the external part (PE 10) was 6 cm and the internal part (PE 5) was 8 cm. Before insertion, patency and absence of leakage of the catheter were tested with a saline flush. To confirm correct placement of the catheters, 10 μl of 2% lidocaine were injected, followed by a 10-μl 0.9% saline flush the day after surgery. All animals developing a bilateral motor block of the hind limbs within 30 s were included in the study. After operation and testing with lidocaine, the animals recovered for at least 5 days. Animals with a deficit in fore- or hind-limb function or other obvious neurologic damage were excluded from study. Each animal was studied twice for thermal testing experiments with a 5-day interval between studies and only once in the postoperative model, on the day of paw incision.

**Drugs**

The following drugs were used in the study: adenosine (Adenocard, FujiSawa, Deerfield, IL), clonidine hydrochloride, phenolamine methanesulfonate salt, and phencyclidine (Sigma Chemical Co., St. Louis, MO), and neostigmine methylsulfate (Genentech, Irvine, CA). Adenosine and neostigmine were used in the commercially available solution with concentrations of 3 mg/ml and 1 mg/ml, respectively, and diluted with saline solution as needed. All other drugs were dissolved in normal saline solution and were injected intrathecally over 30 s in a volume of 5 μl, followed by a 10-μl flush.

**Nociceptive Testing**

Acute thermal antinociception was measured using a commercially available paw withdrawal stimulator. Rats were placed in a clear plastic container on a raised floor of clear, heat-tempered glass and allowed to habituate to the environment for 30–45 min. Then, a radiant heat source was focused on the plantar surface of one hind paw every 15 min, and the latency to paw withdrawal was measured. Both paws were tested in random order 1–2 min apart, and the average of their values was used. In absence of a response, a 30-s cutoff was used to limit possible tissue damage after exposure to the stimulus.

Postoperative mechanical hypersensitivity was tested using a recently described model, in which hypersensitivity to punctate stimuli persisted for several days. Rats with intrathecal catheters implanted 5 days previously were anesthetized with 2% halothane in oxygen/air via a face mask, and after sterile preparation with iodine and draping, a 1-cm longitudinal incision was made with a #11 scalpel blade through skin and fascia of the plantar aspect of the right foot as previously described. The skin was closed with two sutures of 5-0 nylon, and the wound site was covered with a mixture of polymixin B, neomycin, and bacitracin ointment. After surgery, animals were allowed to recover in their cages. Two hours after surgery, rats were placed on an ele-
vated plastic mesh floor in a clear plastic container and allowed to acclimate. Withdrawal responses to punctate mechanical stimulation were determined using calibrated von Frey filaments applied from underneath the cage through openings in the plastic mesh floor to an area adjacent to the wound at the heel. Starting with 41 mM, filaments were applied in a consecutive fashion, ascending or descending. In the absence of a paw withdrawal response to the initially selected filament, a stronger stimulus was presented; in the event of a paw withdrawal, the next weaker stimulus was chosen. Withdrawal threshold was calculated using the Dixon up-down paradigm. A cutoff of 456 mM was used and recorded even if there was no response to this force. Tests were done in duplicate, with a 5-min, test-free period between withdrawal responses, and their median was used. All rats were tested only on the day of paw incision surgery. The order of drug testing was randomized, but the investigator was not blinded to drug or dosage.

Altered behavior (immobility, urination, defecation, grooming) was noted, if present, after drug administration but was not examined systematically or quantified in this study.

Study Paradigm

After connection of intrathecal catheters with tubing and prefilled syringes, rats were allowed to habituate to the test environment. In all experiments, baseline response latencies or withdrawal thresholds were determined before any drug injection. Animals then received cumulative dosing, in 30-min intervals, of intrathecal adenosine (10, 30, 100 µg), clonidine (5, 15, 50 µg), or neostigmine (0.5, 1.5, 5 µg). Timing of cumulative injections was determined by pilot experiments with each drug alone and the combinations. Thermal paw withdrawal latencies were determined every 15 min, and values obtained at 30 min after each dose were taken as the value for that dose. In separate groups of animals that had undergone paw incision on that same day, mechanical withdrawal thresholds were determined before paw incision surgery, before drug injection, and then every 30 min before injection of the next dose. Each group of rats contained 6–12 animals.

Isobolographic analyses were performed to determine the degree of interaction between adenosine and clonidine and adenosine and neostigmine in thermally evoked acute nociception as well as in postoperative mechanical hypersensitivity. Dose-response curves were constructed from % maximum possible effect (MPE) and the dose producing a 50% MPE (ED₅₀) was calculated for each drug for antinociception as was the dose producing a 25% MPE (ED₂₅) in reducing postoperative hypersensitivity. %MPE was defined as: 100 × (postdrug response − predrug response) / (cutoff time or threshold − predrug response). Using an ED₂₅ was necessary because maximal effects in the postoperative model in the dose range studied were ≤ 50% MPE. For drug combination dose responses, drugs were tested in a constant ratio (either of their ED₅₀ for thermal studies or ED₂₅ for postoperative studies). In the case of adenosine for acute thermal nociception, which is lacking efficacy when administered alone, the upper limit for interaction studies was arbitrarily chosen to be a cumulative dose of 30 µg.

Two antagonist studies were performed. To test whether the postoperative effect of adenosine involved spinal α-adrenergic receptor stimulation, 30 µg of intrathecal phen tolamine was injected with every dose of adenosine in the postoperative model. To test adenosine-induced vasodilation as an explanation for its lack of enhancement of neostigmine in the thermal tests, 15 µg of intrathecal phenylephrine was coadministered with every dose of adenosine and neostigmine during thermal testing.

Statistics

Data are presented as mean ± SD, except for paw withdrawal thresholds, which are presented as median and 25th–75th percentiles. ED₅₀ was calculated by linear regression. For the postoperative model, the isobolograms were constructed as previously described. In isobolograms, the theoretical additive point lies on a line connecting the ED₂₅ or ED₅₀ values of the individual doses. Experimental values that lie on or near that line are considered to have additive interactions. Values that lie below and to the left of this additive line are considered to be synergistic, whereas values that lie above and to the right of that line demonstrate a less than additive interaction. The difference between the theoretical additive point and the experimentally determined value was compared using the Student t test. In the case of one drug lacking efficacy (adenosine to acute thermal stimulation), any significant shift in the other agent’s dose response demonstrates synergy.

Results

Thermal Testing

Clonidine and neostigmine, but not adenosine, produced antinociception to thermal testing (fig. 1). The
ED₅₀ values were 19 ± 6 μg for clonidine and 3 ± 1.2 μg for neostigmine. Clonidine and adenosine were associated with substantial diuresis and some sedation (decreased spontaneous exploring activity, but still responsive to acoustic or tactile stimuli), and neostigmine was associated with tail grooming and licking behavior. Motor activity appeared normal in all animals, as animals moved and ambulated normally in and outside the containers.

Intrathecal adenosine synergistically enhanced antinoceception from intrathecal clonidine, reducing its ED₅₀ from 19 ± 6 μg to 4.1 ± 3.1 μg (fig. 2). Animals in this group exhibited intense urination and sedation. In contrast, intrathecal adenosine did not affect antinoceception from intrathecal neostigmine (fig. 2: ED₅₀ of neostigmine alone = 3.0 ± 1.2 and with adenosine = 2.7 ± 1.3). Frequently observed side effects were grooming and licking behavior and urination. Addition of the α₁-adrenergic agonist phenylephrine to every adenosine-neostigmine dose also failed to increase the antinoceptive effect (ED₅₀ of adenosine + neostigmine = 2.7 ± 1.3 μg and adenosine + neostigmine + phentolamine = 3.3 ± 0.9 μg).

Postoperative Hypersensitivity

In all groups the mean withdrawal threshold to von Frey filaments decreased from 456 mN (cutoff) before surgery to 39 mN after incision. Intrathecal administration of clonidine, neostigmine, and also adenosine resulted in a dose-dependent increase in withdrawal thresholds (fig. 3). Phentolamine coadministered with adenosine completely abolished the antihypersensitivity effect of adenosine in all doses used (%MPE was 0 ± 1, 1 ± 1, and 1 ± 1% after adenosine; 10, 30, and 100 μg, respectively; P = NS). Because maximal effects of the given doses of adenosine, clonidine, and neostigmine were 50% MPE or less, only an ED₅₀ could be calculated with precision. According to relative potencies in single drug experiments, the dose ratios in the combination

![Graph](image-url)

**Fig. 1.** Log dose-response curves for the effects of intrathecally administered adenosine, neostigmine, and clonidine on the thermal nociceptive threshold. The response is presented as % maximum possible effect (%MPE) versus log dose in micrograms. Each point on the graph represents the mean ± SD for 6–12 rats.

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**Fig. 2.** % Maximum possible effect (%MPE) from intrathecal clonidine (upper panel) and neostigmine (lower panel) alone and without the addition of adenosine in a fixed ratio. Each value represents the mean ± SD for 6–12 rats.
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Fig. 3. % Maximum possible effect (%MPE) from intrathecal adenosine, neostigmine, and clonidine on punctate mechanical hyperalgesia caused by a plantar incision. Each point on the graph represents the median with error bars showing the 25th and 75th percentile for 6–12 rats.

Experiments were adenosine:neostigmine = 37:1 and adenosine:clonidine = 5:1. In the neostigmine-adenosine group, the effect of the combined drugs was significantly greater than the calculated additive effect (fig. 4A), yielding synergy. In contrast, the experimentally determined ED$_{25}$ for the antihypersensitivity response of the clonidine-adenosine mixture was not different from the theoretical additive ED$_{25}$ of these two drugs (fig. 4B). Side effects were similar to those observed with acute thermal testing of these compounds.

Discussion

These data demonstrate that intrathecal adenosine lacks antinociceptive efficacy by itself but synergistically enhances antinociception from intrathecal clonidine in a rat model of acute thermal nociception. In addition, these data provide the first evidence of efficacy of adenosine, clonidine, and neostigmine and their interactions in a rat model of postoperative hypersensitivity. It is important to qualify these observations with the understanding that some of these agents produced sedation, which could have interfered with the behavioral endpoints of these tests.

Adenosine and Its Interactions with Clonidine and Neostigmine in Acute Pain

In contrast to previous studies with synthetic adenosine receptor agonists, which revealed dose-dependent antinociception to acute noxious stimuli in rats$^{1,3}$ and in spinal dorsal horn neuronal responses,$^{25}$ adenosine itself is inactive. Adenosine’s hydrophilic might have caused a poor penetration of the drug into the spinal cord, resulting in a too small concentration of adenosine reaching the cord to be effective alone against acute thermal stimulation. In contrast, its efficacy alone in the postoperative hypersensitivity model may reflect increased sensitivity to even these low concentrations in this model, a difference in sensory stimuli used (heat in normal animals vs. mechanical stimulation after surgery), or different intensities of stimulation in the two models. That adenosine may have poorly penetrated the spinal cord is consistent with the observation that synthetic adenosine analogs,$^{26}$ but not adenosine itself (current study), produces motor weakness and blockade. Adenosine’s activity on both A1 and A2 receptors in the spinal cord might be another possible reason for its lack of antinociception. Although selective A2-agonists were shown to have no antinociceptive effect,$^{27}$ spinal adenosine A1 receptors have been clearly identified to mediate the inhibition of nociceptive input into the dorsal spinal cord.$^{28}$ This possibility seems less likely because intrathecally administered N-ethylcarboxamide-adenosine (NECA), which has an equal affinity for A1 and A2 receptors, showed antinociceptive effects in the tail immersion test in the rat.$^1$

The observation that the combination of the α$_2$-adrenergic agonist clonidine and adenosine yields synergy is consistent with previous reports with synthetic adenosine analogs.$^5,6$ In general, a supraadditive interaction may result from the administration of two drugs that produce their effects by different receptor mechanisms of action. Adenosine receptor activation in the spinal cord is proposed to produce antinociception by at least two different mechanisms: (1) presynaptic inhibition of excitatory neurotransmitter release with subsequent reduction of substance P concentrations in cerebrospinal fluid,$^{29}$ and (2) postsynaptic inhibition of the effects of excitatory neurotransmitters.$^{30}$ Intrathecal α$_2$-adrenergic agonists mimic the effects of endogenous norepinephrine and produce antinociception by (1) decreasing the release of substance P from primary afferent nerve ter-
Fig. 4. (A) Isobologram at the ED$_{25}$ level for the interaction between adenosine and neostigmine in the postoperative paw incision model when coadministered in a fixed dose ratio. The straight line connecting the single drug ED$_{25}$ points is the theoretical additive line. The experimental point for adenosine—neostigmine mixture was found to be significantly below the theoretical additive line, indicating synergistic interaction. *P < 0.05 versus theoretical additive point. Each point on the graph represents the mean ± SD for 6–12 rats. (B) Isobologram at the ED$_{25}$ level for the interaction between adenosine and clonidine in the postoperative paw incision model when coadministered in a fixed dose ratio. The straight line connecting the single drug ED$_{25}$ points is the theoretical additive line. The experimental point for adenosine—neostigmine mixture was found to be close to the theoretical additive line, indicating additive interaction. Each point on the graph represents the mean ± SD for 6–12 rats.

duced antinociception to acute thermal stimulation. Neostigmine inhibits the breakdown of endogenously released acetylcholine, which has been shown to cause antinociception by stimulation of muscarinic$^{10,54}$ and nicotinic$^{35,50}$ receptors in the spinal cord. Because rats exhibit tonic spinal cholinergic activity,$^9$ intrathecally administered cholinesterase inhibitors alone cause antinociception in this species.$^{34}$

It is unexpected that adenosine's interactions with clonidine and neostigmine differ because spinal $\alpha_2$-adrenergic stimulation produces antinociception in part by causing acetylcholine release from spinal cholinergic interneurons.$^7,8,37$ One possible explanation for the different interaction between adenosine and neostigmine could be a pharmacokinetic effect, whereby vasodilation induced by adenosine resulted in more rapid clearance of neostigmine, masking a potentiating effect. We tested this hypothesis by adding phenylephrine to the neostigmine-adenosine combination to induce powerful vasoconstriction$^{58}$ and observed no difference in this drug interaction.

Differing interactions between adenosine and clonidine compared with neostigmine reinforce our previous hypothesis$^7$ that clonidine must be working through multiple mechanisms to produce antinociception to acute stimulation, not just stimulation of acetylcholine release.

Adenosine and Its Interactions with Clonidine and Neostigmine in a Rat Model of Postoperative Hypersensitivity

The recently developed animal model of incisional pain$^{12}$ closely mimics in time course the human postoperative pain experience. The hypersensitivity to mechan-
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Adult animals in this rat model may represent alldynia because behavior is elicited after surgery from a level of stimulation that fails to elicit behavior preoperatively. Some electrophysiologic experiments demonstrate that a surgical incision in rats induces central sensitization with subsequent mechanical hypersensitivity observed in behavioral studies. The input from primary afferent fibers during and up to 1 h after surgery appears to be the major stimulus for the induction of postoperative hypersensitivity. Thus, this model may offer advantages over previously established tissue or nerve injury models in predicting the ability of spinally administered agents to block central sensitization to reduce postoperative pain. Of course, peripheral inflammation also occurs in this model, and one cannot exclude in the current experiments a peripheral component to the hypersensitivity and its response to drugs administered.

Adenosine itself is active in the postoperative hyperactivity model. Synthetic adenosine receptor agonists decrease thermal and inflammatory hyperalgesia, tactile alldynia, and chronic central pain in animals. The clinical relevance of adenosine's potential as an antihypersensitivity agent is further supported by a case report in which intrathecal administration of a selective A1 adenosine agonist successfully abolished alldynia in a patient with chronic neuropathic pain. When administered to human volunteers, 500-2,000 μg of intrathecal adenosine itself has no effect on pain from ice water immersion of the foot but reduces ischemic tourniquet pain and mechanical hyperalgesia from mustard oil application, consistent with the current study in rats.

Although the role of adenosine receptors in spinal processes involving central sensitization is not well understood, N-methyl-D-aspartate (NMDA) receptors are known to play a key role in the process of central sensitization, and there is a close functional relationship between adenosine A1 and NMDA receptors in the spinal cord. Adenosine analogs suppress dorsal horn neuronal sensitization by subcutaneous formalin or mustard oil application to a region of skin adjacent to their receptive fields. In addition, adenosine reduces excitatory neurotransmitter release from nociceptive stimulation, as described previously. Because injury-induced hypersensitivity is associated in an arthritis model with chronic spinal glutamate and aspartate release, it is conceivable that adenosine's antihypersensitivity effect reflects a reduction in ongoing excitatory neurotransmitter release.

Another possible explanation for adenosine's increased potency in the postoperative state could reflect an interaction with endogenously released norepinephrine. In rats, peripheral nerve stimulation at C-fiber intensity causes an increase in lumbar spinal cord norepinephrine release, measured by microdialysis, and this increase is reduced by thoracic spinal cord transection. Similarly, painful stimulation in sheep increased cerebrospinal fluid concentrations of norepinephrine. Thus, adenosine could have enhanced endogenously released norepinephrine after paw incision to produce an increased antihypersensitivity effect. Adenosine's postoperative antihypersensitivity effect was completely blocked by coadministration of phenolamine, an α-adrenergic antagonist, supporting this hypothesis.

α2-Adrenergic agonists are potent in alleviating alldynia in an animal model of nerve injury, and epidural clonidine powerfully alleviates intractable cancer pain in patients. Our findings in the postoperative model in rats are consistent with human clinical data and these animal studies. Unlike acute thermal antinociception, intrathecal clonidine failed to interact synergistically with intrathecal adenosine to relieve postoperative hypersensitivity. Perhaps this finding reflects the adrenergic mechanism of adenosine's antihypersensitivity effect in the postoperative period, described previously, which would not be expected to interact synergistically with the adrenergic mechanism of clonidine.

Neostigmine and muscarinic agonists reduce alldynia from inflammation. In sheep, intrathecal neostigmine has been a more effective antinociceptive agent in the acute postoperative period than at times more remote from surgery, suggesting that postoperative pain could trigger an increased cholinergic tone in that species. Intrathecal neostigmine produces postoperative analgesia for a variety of surgical procedures in humans, but side effects, such as nausea and vomiting, limit its clinical usefulness.

Unlike antinociception to acute noxious thermal stimulation, intrathecal neostigmine interacted synergistically with adenosine to reduce postoperative hypersensitivity. Because α2-adrenergic agonists interact synergistically with neostigmine, this finding could again reflect an adrenergic component of adenosine's mechanism of action in the postoperative model and would provide a rationale for investigating this interaction in postoperative patients.

Clinical Implications

In the postoperative period, pain evoked by coughing or deep breathing after upper abdominal or thoracic surgery leads to the potentially dangerous conse-
quences: hypoventilation, atelectasis, and hypoxemia, whereas spontaneous pain at rest is generally easy to control. It has been argued that interventions that are effective in modifying punctate hypersensitivity tested by the postoperative paw incision model are likely to have a substantial effect on this aspect of postoperative pain. One approach to improve analgesia and reduce side effects at the same time is to combine small doses of analgesics that interact synergistically to produce analgesia without increasing side effects. The purpose of this study was not to investigate side effects of these agents alone and in combination. Because side effects were often observed to each of these drugs alone and in combination, one cannot conclude from these data that such combinations will be clinically useful. Finally, although the commercially available preparation of adenosine in the United States does not contain preservatives, it is inappropriate to administer adenosine intrathecally to humans before a toxicologic assessment has proven it to be innocuous in at least two animal species.

In summary, intrathecal administration of adenosine alone causes no antinociception to a thermal stimulus in rats but enhances antinociception from intrathecal clonidine. A lack of improved antinociception combined with the cholinesterase inhibitor neostigmine to adenosine further suggests that the cholinergic pathway does not essentially contribute to clonidine's antinociception to acute thermal stimulation. Adenosine, clonidine, and neostigmine alone produce dose-dependent, antihyperensitivity effects in a postoperative rat model. Synergistic interaction of adenosine and neostigmine in this paradigm and additive effects of adenosine and clonidine support the hypothesis that spinal cord noradrenergic systems are activated in response to surgery. These findings may provide a rationale for combining these drugs for improved human postoperative pain treatment in the future.

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