Intrathecal and Epidural drug injections : Not only Bupivacaine or Lidocaine and Not only Anesthesia or Analgesia

Joseph Eldor, MD

The concept that a barrier exists between the blood and the brain was first formulated nearly a century ago. Colored dyes injected into the circulation of laboratory animals stained all tissues except the brain. However, when the same dyes were introduced into cerebral spinal fluid (CSF), the liquid that bathes, nourishes, and cushions the brain and spinal cord, brain cells were readily stained. Clearly, something was preventing these dyes from escaping from the blood vessels in the brain, although they readily leaked from the vessels throughout the rest of the body.

One way to bypass this blood brain barrier is to inject the drug into the intrathecal or epidural spaces. It is done in the operating rooms, delivery rooms, radiology departments, oncology departments and should take its place in other specialties which do not have such a long experience with this method like Anesthesiology.

In order to highlight this treatment modality from various aspects the Medline was searched for drugs injected intrathecally or epidurally, intentionally or inadvertently, in the years 1999-2000.

This Spinal Therapy method should involve specialties like Neurology, Cardiology, Psychiatry, etc., since the brain and its spinal cord is where the drugs should act in order to cure or ameliorate many diseases and ailments.

Some examples of this Spinal Therapy:

1. Epidural blood patch as a treatment for headache after dural puncture.
2. Genetically modified neural stem cells, acting as a source of neurotrophic factors, have the potential to participate in spinal cord repair.
3. Accidental epidural administration of potassium chloride.
4. Intrathecal ethanol block is a last but very useful choice for treatment of intractable spasticity in PML and other neurologic disorders in AIDS patients when other oral treatments have failed and intrathecal baclofen infusion is not suitable.
5. Altered spinal GABA levels contribute to the induction phase of chronic neuropathic pain and that early intervention to restore GABA may prevent the development of that pain.
6. Intrathecal methylprednisolone for postherpetic neuralgia.
7. Continuous intrathecal delivery of baclofen will control spastic hypertonia caused by long-standing cerebral palsy (CP).
8. Intrathecal clonidine and lidocaine dose-dependently produced antinociception in the formalin test.

9. Continuous intrathecal administration of nicardipine using a portable infusion pump system for management of vasospasm after subarachniod hemorrhage.
10. Intrathecal cannabinoid administration suppresses noxious stimulus-evoked Fos protein-like immunoreactivity in rat spinal cord.
11. Epidural naloxone reduces epidural morphine-induced intestinal hypomotility without reversing its analgesic effects.
12. Intrathecal endomorphin-1 produced antinociception in a dose-dependent manner in the rat tail flick, tail pressure and formalin tests, which was mediated by spinal mu-opioid receptors and modulated by alpha 2-adrenoceptors.
13. Unmodified PNA (Peptide nucleic acids) applied i.t. appears to function as an effective antisense reagent in rat spinal cord in vivo.
14. Intrathecal use of colistin.
15. Computed tomography of spinal cord after lumbar intrathecal introduction of metrizamide (computer assisted myelography).
16. Acute Respiratory distress syndrome (ARDS) is a rare complication following intrathecal (IT) injection of methotrexate (MTX) in adult acute lymphoblastic leukemia (ALL) patients.
17. Intrathecal mitozantrone has to be prohibited.
18. Coadministration of intrathecal strychnine and bicuculline effects synergistic allodynia in the rat.
19. Intrathecal administration of 4-aminopyridine at a rate of 5 microg/h does not appear to cause adverse effects and may modify spinal cord function. This route of administration allows local cerebrospinal fluid concentrations equivalent to those produced by maximum tolerable systemic doses, which require 1000 times more drug substance to be delivered to the subject as a whole. Intrathecal administration offers the potential to focus therapeutic effects to the lesion site while minimizing systemic side effects.
20. Epidural 3% 2-chloroprocaine without epinephrine is an advantageous choice for ambulatory knee arthroscopy. It enables readiness for discharge an hour sooner than 1.5% lidocaine, requires fewer reinjection interventions, and may reduce delayed discharge secondary to prolonged time to void.
21. Intraspinal injection of quisqualic acid (QUIS) produces excitotoxic injury with pathophysiological characteristics similar to those associated with ischemic and traumatic spinal cord injury (SCI). Interleukin-10 (IL-10), a potent anti-inflammatory cytokine, is able to reduce mRNA levels of inflammatory and cell death-related genes leading to a reduction of pain behaviors.
22. If intrathecal diamorphine is used in combination with rectal diclofenac and without oral analgesia, then 1 mg provides superior analgesia to 0.5 mg without any worsening of the side-effects.
23. Intrathecal treatment of neoplastic meningitis due to breast cancer with a slow-release formulation of cytarabine.
24. The novel AK (adenosine kinase) inhibitor A-134974 potently reduces thermal hyperalgesia primarily through interactions with spinal sites, whereas its ability to depress locomotor activity is predominantly mediated by supraspinal sites.

25. Intrathecal gabapentin is effective against tactile allodynia that occurs after paw incision, and interacts synergistically with clonidine.
26. Intrathecal MPV-2426 has spatially limited antinociceptive properties in neuropathic and non-neuropathic conditions because of its action on spinal alpha2-adrenoceptors. These properties may be advantageous when designing therapy for spatially restricted pain problems.
27. Administration of intrathecal opioid and an alpha2-agonist can be effective in the treatment of the pain of erythromelalgia and offers an alternative pain treatment modality for patients with unremitting pain refractory to more conservative therapy.
28. Comparison of extradural injections of lignocaine and xylazine in azaperone-sedated pigs.
29. Optimized therapy of spastic syndrome by combination intrathecal baclofen with botulinum toxin.
30. Despite decreased postoperative morphine requirements, intrathecal morphine administration did not have a clinically relevant effect on extubation time after CABG surgery. This study suggests that 250 microg is the optimal dose of intrathecal morphine to provide significant postoperative analgesia without delaying tracheal extubation.
31. The analgesic effects of i.v. and i.t. sufentanil are similar, probably because sufentanil is highly soluble in lipids. Sufentanil-induced facilitations relate to supraspinal actions on motor controls and/or on the descending control of nociceptive transmission.
32. The combined spinal administration of mu opioids and N-type calcium channel blockers may be useful in providing analgesia for A delta mediated (first, sharp) pain while minimizing the side effects of both drugs.
33. A single dose of dexamethasone (10 mg) did not potentiate the analgesic effect or reduce the incidence of PONV after intrathecal injection of tetracaine and neostigmine.
34. Intrathecal MX2 would be a safe and effective method for treating dissemination of malignant glioma.
35. Since evidence points to the involvement of cholecystokinin (CCK) in nociception, the effect of intrathecal CI-988, an antagonist of the CCK-B receptors, were examined on mechanical hyperalgesia and allodynia in normal, mononeuropathic and diabetic rats. Results show the CCK-B receptor blockade-mediated antinociceptive effects and reveals the antinociceptive action of morphine in diabetic rats after CCKergic system inhibition.
36. Intrathecal cyclooxygenase inhibitor administration attenuates morphine antinociceptive tolerance in rats.
37. Masculine copulatory behavior is facilitated by intrathecally administered muscarine.
38. Extrapyramidal reactions after epidural droperidol.
39. Continuous intrathecal fluid infusions elevate nerve growth factor levels and prevent functional deficits after spinal cord ischemia.
40. Intrathecal administration of thrombin inhibitor ameliorates cerebral vasospasm.

41. Intrathecal Zn2+ attenuates morphine antinociception and the development of acute tolerance.
42. Neuropeptide FF attenuates allodynia in models of chronic inflammation and neuropathy following intrathecal or intracerebroventricular administration.
43. Modification of cardiovascular response of adenosine A2 receptor agonist by adenylate cyclase in the spinal cord of rats.
44. Ziconotide has a favourable risk/benefit ratio with advantages over several currently available intrathecal therapies for pain.
45. Antagonism of the melanocortin system reduces cold and mechanical allodynia in mononeuropathic rats.
46. Regeneration of lesioned corticospinal tract fibers in the adult rat induced by a recombinant, humanized IN-1 antibody fragment.
47. Regeneration of lesioned corticospinal tract fibers in the adult rat induced by a recombinant, humanized IN-1 antibody fragment.
48. Treatment of a vancomycin-resistant Enterococcus faecium ventricular drain infection with quinupristin/dalfopristin.
49. Endomorphin-1 and endomorphin-2 may produce antinociception through different subtypes of mu-opioid receptor.
50. Caudal S(+)-ketamine provided more effective analgesia than did intramuscular S(+)-ketamine, indicating a local analgesic effect.
51. Regulation of the development of allodynia by intrathecally administered P2 purinoceptor agonists and antagonists in mice.
52. Spinal dynorphin promotes abnormal pain and acts to reduce the antinociceptive efficacy of spinal opioids (i.e., tolerance).
53. Intrathecal human anti-tetanus immunoglobulin in the management of tetanus.
54. Spinal administration of acetaminophen to mice produced dose-related, naloxone-insensitive antinociception.
55. Effect of intrathecal injection of dopamine receptor agonists/antagonists on pain and acupuncture analgesia in rats.
56. After total hip replacement, administration of intrathecal nalbuphine resulted in a significantly faster onset of pain relief and shorter duration of analgesia than intrathecal morphine.
57. Spinal anandamide inhibits nociceptive transmission via cannabinoid receptor activation in vivo.
58. In patients with recently ruptured aneurysms, GDC (Guglielmi detachable coil) placement followed by immediate intrathecal administration of UK (urokinase) from the cisterna magna may be a safe and reasonable means of preventing vasospasms and may result in improved treatment outcomes.
59. Intrathecal adenosine administration in abdominal hysterectomy lacks analgesic effect.
60. Anesthesia with injection of cocaine into the spinal canal.
61. Spinal mechanisms underlying A-85380-induced effects on acute thermal pain.
62. Spinal ibuprofen blocks opioid withdrawal hyperalgesia in the rat in a stereospecific fashion, implicating the likely release of spinal prostaglandins during withdrawal and their possible role as

neuromodulators in the enhancement of nociception that accompanies this phenomenon.
63. Effects of radolmidine, a novel alpha2 -adrenergic agonist compared with dexmedetomidine in different pain models in the rat.
64. Modulatory role of ginsenosides injected intrathecally or intracerebroventricularly in the production of antinociception induced by kappa-opioid receptor agonist administered intracerebroventricularly in the mouse.
65. Antinociceptive mechanisms of dipsacus saponin C administered intrathecally in mice.
66. The intrathecal injection of 1.6 microg/kg of oxytocin is associated with minimal hemodynamic effects during isoflurane anesthesia.
67. The spinal antinociceptive effect of FR140423 is mediated through kyotorphin receptors.
68. The effect of intrathecal endomorphin-2 on the flexor reflex in normal, inflamed and axotomized rats: reduced effect in rats with autotomy.
69. Intrathecal MPV-2426 dose-dependently attenuates postoperative hyperalgesia to mechanical stimulation because of an action on alpha2 adrenoceptors. Its antihyperalgesic action is as effective as that produced by dexmedetomidine and is considerably stronger than that produced by clonidine. However, preoperative treatment with MPV-2426 does not prevent the development of postoperative hyperalgesia.
70. Medullary and intrathecal injections of 17beta-estradiol in male rats.
71. Surgical analgesia of the flank of goats was achieved after lumbosacral epidural administration of 20 micrograms medetomidine/kg, diluted in 5 ml of sterile water.
72. Accidental injection of thiopental into the epidural space.
73. Intrathecal sodium nitroprusside improves cerebral blood flow and oxygenation in refractory cerebral vasospasm and ischemia in humans.
74. Intrathecal injection of corticotropin inhibited nitric-oxide synthase-positive neuron increase in rat spinal cord after formalin-induced hyperalgesia.
75. Intrathecal cytarabine and bone marrow suppression.
76. In vitro testing shows that tonicaine displays a higher affinity for the local anesthetic binding site than does lidocaine; in vivotesting indicates that tonicaine elicits sensory blockade of a duration significantly longer than that elicited by bupivacaine. Tonicaine, however, has a narrow therapeutic index, with substantial neurotoxicity at 1 mm in rats, and may have limited clinical value.
77. Intrathecally administered spermine produces the scratching, biting and licking behaviour in mice.
78. Intrathecal administration of 5-fluoro-2'-deoxyuridine for treatment of meningeal dissemination of malignant tumors.
79. Long-term intrathecal administration of glycine prevents mechanical hyperalgesia in a rat model of neuropathic pain.
80. Intrathecal busulfan treatment of human neoplastic meningitis in athymic nude rats.
81. Delivery of AraC (14C-cytosine arabinoside) to brain parenchyma by the IV, IT or IVT routes will be subtherapeutic. Delivery by CED (convection-enhanced delivery (CED) into the caudate nucleus) can

achieve, and maintain, therapeutic levels of AraC in the brain, and should be further evaluated as a potential method of drug delivery.
82. Effects of spinally administered P2X receptor agonists and antagonists on the responses of dorsal horn neurones recorded in normal, carrageenan-inflamed and neuropathic rats.
83. Intrathecal lithium reduces neuropathic pain responses in a rat model of peripheral neuropathy.
84. Intrathecally administered cGMP-dependent protein kinase Ialpha inhibitor significantly reduced the threshold for isoflurane anesthesia.
85. Intrathecal administration of MgSO(4) may be therapeutically beneficial for patients with tonic pain involving the spinal NMDA receptors.
86. Effect of intrathecal administration of serotonin in chronic pain models in rats.
87. Effects of intrathecal nocistatin on the flexor reflex and its interaction with orphanin FQ nociceptin.
88. Prevention of neuroleukemia by intrathecal administration of cytosar and methotrexate in acute lymphoblastic leukemia in adults.
89. Iopromide 240 and iohexol 240 are equally safe and effective and can be recommended for myelography.
90. Intrathecal depot cytarabine therapy: a welcome addition to a limited armamentarium.
91. Both subcutaneous and intrathecal treatment of rHuLeptin (recombinant human leptin) was associated with effects on body weight, food intake, and body fat in dogs. These results support the concept that the central nervous system is the probable primary site of action for leptin and suggest that rHuLeptin has similar physiologic activities that influence body weight, body fat, and metabolism in large animals to those reported previously in rodents.
92. Nociceptin (1 - 7) antagonizes nociceptin-induced hyperalgesia in mice.
93. The 10-microg intrathecal neostigmine dose alone produced no analgesia or side effects, but reduced the ED50 of intrathecal sufentanil by approximately 25%.
94. Volume had no significant influence on either cephalad spread or duration of sensory blockade for either isobaric or hyperbaric bupivacaine. Time for offset of anesthesia was shorter with hyperbaric bupivacaine compared with isobaric solutions.
95. Intrathecal ropivacaine 12 mg is approximately equivalent to bupivacaine 8 mg. At this dose, ropivacaine offers no significant advantage compared with bupivacaine.
96. Addition of intrathecal midazolam to bupivacaine produces better post-operative analgesia without prolonging recovery.
97. Epidural administration of RTX (Resiniferatoxin, an ultrapotent capsaicin analog) at the lumbar spinal level produces profound, long-lasting, segmental analgesia to C-fiber mediated pain in the rat.
98. Intrathecal gadolinium-enhanced MR myelography and cisternography.
99. Early treatment with IT thio-TEPA may result in improved survival with minimal morbidity.

100. Antinociception produced by systemic, spinal and supraspinal administration of amiloride in mice.
101. The use of 0.1 mg intrathecal morphine plus NSAIDs provides analgesia of similar quality to 0.25 mg but with fewer undesirable side effects following Cesarean section.
102. Bromage PR : The epidural potato - and beyond.
103. Yaksh TL : A drug has to do what a drug has to do.

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Anesth Analg 1999 Nov;89(5):1075-7

Comment on:

- Anesth Analg. 1999 Nov;89(5):1233-5

A drug has to do what a drug has to do.

Yaksh TL.

Publication Types:

- Comment
- Editorial

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Anaesthesia 1999 Jun;54(6):619-20

The epidural potato - and beyond.

Bromage PR.

Publication Types:

- Letter

PMID: 10404195 [PubMed - indexed for MEDLINE]

Eur J Anaesthesiol 1999 May;16(5):298-303

Seven-year review of requests for epidural blood patches for headache after dural puncture: referral patterns and the effectiveness of blood patches.

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A review was undertaken of all 190 patients who were referred over 7 years, from 1991 to 1997 inclusive, for an epidural blood patch as a treatment for headache after dural puncture. The patterns of referral and symptoms, the distributions of age and gender and the effectiveness of the blood patch were examined. Most of the referrals (n = 153) were after deliberate diagnostic dural puncture in neurology and neuroradiology, with a minority (n = 28) used for anaesthesia and obstetrics, which were mostly inadvertent. Another nine cases were related to placement of an intrathecal catheter. The numbers of referrals per year reached a maximum in 1995 before falling again, a curious inverse relation to the number of invasive neuro-radiological diagnostic procedures. Most of the patients were between 30 and 50-years-old, with 25 younger than 30 and 14 older than 60. Women accounted for 70% of the referrals for headache, although the gender ratio amongst patients subjected to at risk procedures appeared closer to 50:50. Neckache accompanied the headache in 85% of cases, auditory problems were volunteered by three patients and one patient had diplopia for 6 weeks. Of the 190 patients who were referred, 186 received at least one patch, the symptoms in the remaining four being too mild or atypical to warrant blood patch treatment. This provided initial relief in all but two patients, one of whom received a further epidural blood patch with no effect. There was sustained relief of symptoms in 136 and a partial relapse in 38 patients, which resolved without needing any further blood patch. A second patch was provided for seven patients and a third for three patients, of whom two were cured. Of the patients who needed more than one blood patch, nine were after inadvertent dural puncture with a Tuohy needle and, of these patients, six were in labour. A total of 200 patches were provided in all for the 186 patients and all but three patients had a satisfactory outcome. Epidural blood patches are effective in treating headache after dural puncture, but less successful than is commonly believed, especially after inadvertent dural taps. A relapse after treatment does not always require a second patch. Specialities other than anaesthesia seemed reluctant to accept the benefits in both cost and comfort of using needles of improved design for dural puncture.

PMID: 10390664 [PubMed - indexed for MEDLINE]

Exp Neurol 1999 Jul;158(1):9-26

Related Articles, Books, LinkOut

Intraspinal delivery of neurotrophin-3 using neural stem cells genetically modified by recombinant retrovirus.

Liu Y, Himes BT, Solowska J, Moul J, Chow SY, Park KI, Tessler A, Murray M, Snyder EY, Fischer I.

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Neural stem cells have been shown to participate in the repair of experimental CNS disorders. To examine their potential in spinal cord repair, we used retroviral vectors to genetically modify a clone of neural stem cells, C17, to overproduce neurotrophin-3 (NT-3). The cells were infected with a retrovirus construct containing the NT-3.IRES.lacZ/neo sequence and cloned by limiting dilution and selection for lacZ expression. We studied the characteristics of the modified neural stem cells in vitro and after transplantation into the intact spinal cord of immunosuppressed adult rats. Our results show that: (i) most of the genetically modified cells express both NT-3 and lacZ genes with a high coexpression ratio in vitro and after transplantation; and (ii) large numbers of the xenografted cells survive in the spinal cord of adult rats for at least 2 months, differentiate into neuronal and glial phenotypes, and migrate for long distances. We conclude that genetically modified neural stem cells, acting as a source of neurotrophic factors, have the potential to participate in spinal cord repair.

PMID: 10448414 [PubMed - indexed for MEDLINE]

Eur J Anaesthesiol 1999 Jun;16(6):410-2

Related Articles, Books, LinkOut

A clinical diagnosis of inadvertent epidural administration of potassium chloride.

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We present a case of accidental epidural administration of potassium chloride, which was diagnosed by clinical signs. The genesis of symptoms and signs following such administration is discussed and compared with other published reports.

PMID: 10434172 [PubMed - indexed for MEDLINE]

Spinal Cord 1999 Jun;37(6):450-2

Related Articles, Books, LinkOut

Successful intrathecal ethanol block for intractable spasticity of AIDS-related progressive multifocal leukoencephalopathy.

Asensi V, Asensi JM, Carton JA, Maradona JA, Ona M, Arechaga C.

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OBJECTIVE: To study the efficacy of intrathecal ethanol block to relieve intractable spasticity in AIDS-related progressive multifocal leukoencephalopathy (PML) when long-term intrathecal baclofen infusion cannot be used. METHODS: A 33-year-old man with AIDS-related PML developed very severe spastic paraparesis (Ashworth rigidity score, 4) and painful muscle spasms. The patient was unable to sit in his wheelchair and remained bed bound. Combined oral baclofen and tizanidine at therapeutical doses were used without any effect on the spasticity. The patient refused the placement of an intrathecal catheter for long-term baclofen infusion. A single intrathecal ethanol (6 ml) injection in the L2-L3 intervertebral space with the patient placed in a lateral Trendelenburg (40 C) position was performed. RESULTS: The procedure was very effective in improving the stiffness (Ashworth rigidity score. 2, after the technique) and the muscle spasms disappeared. No side effects during or after the injection were observed. CONCLUSION: Intrathecal ethanol block is a last but very useful choice for treatment of intractable spasticity in PML and other neurologic disorders in AIDS patients when other oral treatments have failed and intrathecal baclofen infusion is not suitable.

PMID: 10432267 [PubMed - indexed for MEDLINE]

Brain Res 1999 Jul 24;835(2):334-9 Related Articles, Books, LinkOut

A single intrathecal injection of GABA permanently reverses neuropathic pain after nerve injury.

Eaton MJ, Martinez MA, Karmally S.

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To investigate whether neuropathic pain is sensitive to spinal GABA levels, GABA was injected intrathecally after nerve injury and sensory behaviors were evaluated. Both thermal and tactile hypersensitivities were permanently reversed at the highest doses of GABA. However, if GABA was injected any later than 2-3 weeks after nerve injury, it was ineffective to prevent such hypersensitivity. This suggests that altered spinal GABA levels contribute to the induction phase of chronic neuropathic pain and that early intervention to

restore GABA may prevent the development of that pain. Copyright 1999 Elsevier Science B.V.

PMID: 10415391 [PubMed - indexed for MEDLINE]

N Engl J Med 2001 Mar 29;344(13):1021; discussion 1021-2

Related Articles, Books, LinkOut

NEJM

Intrathecal methylprednisolone for postherpetic neuralgia.

Srinivasan B.

Publication Types:

- Letter

PMID: 11280324 [PubMed - indexed for MEDLINE]

Arch Phys Med Rehabil 2001 Feb;82(2):155-61

Related Articles, Books, LinkOut

Continuously infused intrathecal baclofen over 12 months for spastic hypertonia in adolescents and adults with cerebral palsy.

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OBJECTIVE: To determine if the continuous intrathecal delivery of baclofen will control spastic hypertonia caused by long-standing cerebral palsy (CP). DESIGN: Case series. SETTING: Tertiary care outpatient and inpatient rehabilitation center directly attached to a university hospital. PATIENTS: Thirteen CP patients (average age, 25yr; range, 13--43yr) with intractable spastic hypertonia and quadriparesis (one of whom had predominate diplegia) who had not responded to oral medications including baclofen. INTERVENTION: Patients were screened via a bolus injection of baclofen intrathecally. Those who dropped an average of 2 points on their lower extremity (LE) Ashworth scores were offered computer-controlled pump implantation for 12 months of continuous delivery of intrathecal baclofen (ITB). MAIN OUTCOME MEASURES: Ashworth rigidity scores, spasm scores, and deep tendon reflex scores were collected for both the upper extremities (UEs) and LEs. Differences over time were assessed via descriptive statistics and Wilcoxon's signed-rank test. RESULTS: After 1 year of continuous ITB treatment, the average LE Ashworth score standard

deviation decreased from 3.4 1.2 to 1.5 0.7 (p <.0001), spasm score from 1.4 1.6 to 0.6 1.2 (p =.1024), and reflex score from 2.5 1.2 to 0.7 1.1 (p <.0001). The average UE Ashworth score decreased from 3.0 1.2 to 1.7 1.0 (p <.0001), spasm score from 1.2 1.6 to 0.2 0.6 (p =.0135), and reflex score from 2.3 0.7 to 0.5 0.9 (p <.0001). The average ITB dose required to attain these effects at 1 year was 263 91microg continuously infused per day. CONCLUSION: Continuously infused ITB can reduce spastic hypertonia in the UEs and LEs associated with long-standing CP. This reduction in tone will allow more freedom of movement and the potential for improved function.

PMID: 11239304 [PubMed - indexed for MEDLINE]

Anesth Analg 2001 Mar;92(3):733-8

Antinociceptive interaction between spinal clonidine and lidocaine in the rat formalin test: an isobolographic analysis.

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Clinical and basic science studies suggest that spinal alpha-2-adrenergic receptor agonists and local anesthetics produce analgesia, but interaction between alpha-2-adrenergic receptor agonists and local anesthetics in the persistent pain model has not been examined. In the present study, using isobolographic analysis, we investigated the antinociceptive interaction of intrathecal clonidine and lidocaine in the rat formalin test. Sprague-Dawley rats were implanted with chronic lumbar intrathecal catheters, and were tested for paw flinch by formalin injection. Biphasic painful behavior was counted. Intrathecal clonidine (3-12 nmol) was administered 15 min before formalin, and intrathecal lidocaine (375-1850 nmol) was administered 5 min before formalin. To examine the interaction of intrathecal clonidine and lidocaine, an isobolographic design was used. Spinal administration of clonidine produced dose-dependent suppression of the biphasic responses in the formalin test. Spinal lidocaine resulted in dose-dependent transient motor dysfunction and the motor dysfunction recovered to normal at 10-15 min after administration. Spinal lidocaine produced dose-dependent suppression of phase-2 activity in the formalin test. Isobolographic analysis showed that the combination of intrathecal clonidine and lidocaine synergistically reduced Phase-2 activity. We conclude that intrathecal clonidine synergistically interacts with lidocaine in reducing the nociceptive response in the formalin test. IMPLICATIONS: Preformalin administration of intrathecal clonidine and lidocaine dose-dependently produced antinociception in the formalin test. The combination of clonidine and lidocaine, synergistically produced suppression of nociceptive response in the persistent pain model.

PMID: 11226110 [PubMed - indexed for MEDLINE]

No Shinkei Geka 2001 Jan;29(1):23-30 Related Articles, Books

[Continuous intrathecal administration of nicardipine using a portable infusion pump system for management of vasospasm after subarachniod hemorrhage].

[Article in Japanese]

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We studied the feasibility of intrathecal nicardipine administration using a portable infusion pump system in five cases (two males and three females) of subarachnoid hemorrhage (SAH). All of the five cases manifested severe SAH of Hunt & Kosnic grade 3 or 4, and Fisher CT group 3. Aneurysmal sites of five cases were as follows: three internal carotid-posterior communicating artery (IC-PC) aneurysms and two anterior communicating artery (Acom) aneurysms. The container of the infusion pump system was filled with 105 ml of nicardipine-saline solution (2:1), and this system was connected to the cisternal tube. The solution was continuously injected at a daily dose of 12 ml (8 mg of nicardipine). This therapy was continued for 14 days, and new nicardipine solution was supplied only once at 8 days after the operation during this therapy. No postural restraint of patients was necessary, even during physical movement for rehabilitation. Postoperative angiography was performed in three of five cases at one week after the operation. No angiographic vasospasm was observed in any of the three cases. Symptomatic vasospasm was observed in one case of right IC-PC aneurysm as a transient total aphesia and right hemiplegia, which recovered within several hours due to induced hypervolemia and hypertension therapy. Mild meningitis at 14 days after the operation complicated this treatment in one case, but it improved in a few days after the cisternal tube was removed. It was speculated that meningitis was caused by cerebrospinal fluid leakage from the scalp exit site of the cisternal tube. All of the five cases had obtained good recovery at three months after the operation. These results show that, although this method involves a risk of infection, it has the advantage of easiness and convenience over conventional methods. Though further improvement of this method is required, this preliminary stage is potentially useful for delivering not only nicardipine, but also for other drugs which may be used in intrathecal administration therapy.

PMID: 11218763 [PubMed - indexed for MEDLINE]

Zhongguo Yao Li Xue Bao 1999 Dec;20(12):1132-6

Intrathecal cannabinoid administration suppresses noxious stimulus-evoked Fos protein-like immunoreactivity in rat spinal cord: comparison with morphine.

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AIM: To determine whether cannabinoids suppress noxious stimulus-evoked Fos protein-like immunoreactivity (FLI) through direct actions at the spinal level. METHODS: Rats were implanted with intrathecal (ith) catheters at least one week prior to evaluation in the formalin test. Effects of the cannabinoid agonist, CP55,940 (80 micrograms ith) on formalin pain and FLI in rat spinal cord were compared with that of the prototypic narcotic analgesic, morphine (20 micrograms ith). CP55,940 suppressed pain behavior and FLI induced by intraplantar formalin. The cannabinoid suppressed Fos in the neck region of the dorsal horn and in the ventral horn, but not in the nucleus proprius. The efficacy of the cannabinoid in suppressing FLI in these laminae and pain behavior was comparable to morphine administered via the same route. However, only morphine suppressed FLI in the superficial dorsal horn relative to vehicle treatment. CONCLUSION: Cannabinoids suppress nociceptive processing, in part, through actions at the spinal level. However, morphine showed greater potency and efficacy than CP55,940 in suppressing formalin-induced FLI following spinal administration.

PMID: 11216448 [PubMed - indexed for MEDLINE]

Can J Anaesth 2001 Jan;48(1):54-8

Epidural naloxone reduces intestinal hypomotility but not analgesia of epidural morphine.

Lee J, Shim JY, Choi JH, Kim ES, Kwon OK, Moon DE, Choi JH, Bishop MJ.

Department of Anesthesiology, Kangnam Saint Mary's Hospital, Seoul, Korea.

PURPOSE: Epidural morphine is associated with decreased bowel motility and increased transit time. Low doses of intravenous naloxone reduce morphine-induced pruritus without reversing analgesia, but the effect of epidural naloxone on bowel motility has not been studied. Therefore we evaluated bowel motility and analgesia when naloxone was co-administered with morphine into the epidural space. METHODS: Forty-three patients

having combined thoracic epidural and general anesthesia for subtotal gastrectomy were randomly assigned to one of two study groups. All received a bolus dose of 3 mg epidural morphine at the beginning of surgery, followed by a continuous epidural infusion containing 3 mg morphine in 100 ml bupivacaine 0.125% with either no naloxone (control group, n = 18) or a calculated dose of 0.208 microg x kg(-1) x hr(-1) of naloxone (experimental group, n = 25) for 48 hr. We measured the time to the first postoperative passage of flatus and feces to evaluate the restoration of bowel function, and visual analog scales (VAS) for pain during rest and movement. Scores were assessed at 2, 4, 8, 16, 24, 36 and 48 hr postoperatively. RESULTS: The experimental group had a shorter time to the first postoperative passage of flatus (5 1.9 +/- 1 6.6 hr vs 87.0 +/- 19.5 hr, P < 0.001) and feces (95.3 +/- 25.0 hr vs 132.9 +/- 29.4 hr, P ~ 0.001). No differences were found in either resting or active VAS between the two groups. CONCLUSION: Epidural naloxone reduces epidural morphine-induced intestinal hypomotility without reversing its analgesic effects.

Publication Types:

- Clinical trial
- Randomized controlled trial

PMID: 11212050 [PubMed - indexed for MEDLINE]

Life Sci 2000 Mar 3;66(15):PL195-204 Related Articles, Books

Intrathecal endomorphin-1 produces antinociceptive activities modulated by alpha 2-adrenoceptors in the rat tail flick, tail pressure and formalin tests.

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It is known that spinal morphine produces antinociception that is modulated by alpha 2-adrenoceptors. Endomorphin-1, a newly-isolated endogenous opioid ligand, shows the greatest selectivity and affinity for the mu-opiate receptor of any endogenous substance found to date and may serve as a natural ligand for the mu-opiate receptor. We examined the antinociceptive effects of endomorphin-1 administered intrathecally (i.t.) in the rat tail flick, tail pressure and formalin tests. Intrathecal endomorphin-1 produced dose-dependent antinociceptive effects in the three tests. ED50 (CI95) values for antinociception of i.t. endomorphin-1 in the tail flick test and tail pressure test were 1.9 (0.96-3.76) nmol and 1.8 (0.8-4.2) nmol, respectively. ED50 (CI95) values for phase 1 and phase 2 in the formalin test were 12.5 (7.9-19.8) nmol and 17.5 (10.2-30) nmol, respectively. Pretreatment with i.t. beta-

funaltrexamine (a mu-opioid receptor selective antagonist) significantly antagonized the antinociceptive effects of endomorphin-1 in the three tests. Beta-funaltrexamine alone had not effects on the three tests. The antinociceptive effects of endomorphin-1 were also antagonized by i.t. yohimbine (an alpha 2-adrenoceptor selective antagonist). The combination of ineffective doses of i.t. clonidine (an alpha 2-adrenoceptor agonist) and endomorphin-1 produced a significant antinociception in the three tests. The results showed that intrathecal endomorphin-1 produced antinociception in a dose-dependent manner in the rat tail flick, tail pressure and formalin tests, which was mediated by spinal mu-opioid receptors and modulated by alpha 2-adrenoceptors.

PMID: 11210721 [PubMed - indexed for MEDLINE]

Neuroreport 2001 Feb 12,;12(2):317-20 Related Articles, Books

Intrathecal administration of PNA targeting galanin receptor reduces galanin-mediated inhibitory effect in the rat spinal cord.

Rezaei K, Xu IS, Wu WP, Shi TJ, Soomets U, Land T, Xu XJ, Wiesenfeld-Hallin Z, Hokfelt T, Bartfai T, Langel U.

Department of Neurochemistry and Neurotoxicology, Stockholm University, Sweden.

Peptide nucleic acids (PNA) are nucleic acid analogues containing neutral amide backbone, forming stable and tight complexes with complementary DNA/RNA. However, it is unclear whether unmodified PNA can efficiently penetrate neuronal tissue in order to act as antisense reagent. Here we show that intrathecal (i.t.) injection of an unmodified antisense PNA complementary to the rat galanin receptor type 1 (GalR1) mRNA is able to block the inhibitory effect of i.t. administered galanin on spinal nociceptive transmission. Autoradiographic ligand binding studies using [125I]galanin show that the unmodified PNA is able to reduce the density of galanin binding sites in the dorsal horn. Thus, unmodified PNA applied i.t. appears to function as an effective antisense reagent in rat spinal cord in vivo.

PMID: 11209942 [PubMed - indexed for MEDLINE]

Related Articles, Books, LinkOut

J Clin Microbiol 2000 Sep;38(9):3523

Intrathecal use of colistin.

Vasen W, Desmery P, Ilutovich S, Di Martino A.

Publication Types:

- Letter

PMID: 11203334 [PubMed - indexed for MEDLINE]

AJNR Am J Neuroradiol 2001 Jan;22(1):218-21 Related Articles, Books, LinkOut

Full text article at www.ajnr.org

In re: Di Chiro G, Schellinger D. Computed tomography of spinal cord after lumbar intrathecal introduction of metrizamide (computer assisted myelography).

Wolpert SM.

Publication Types:

- Biography
- Historical article

Personal Name as Subject:

- Di Chiro G
- Schellinger D

PMID: 11201971 [PubMed - indexed for MEDLINE]

Ann Hematol 2000 Dec;79(12):696-9 Related Articles, Books, LinkOut

Annals of Hematology

Acute respiratory distress syndrome following intrathecal methotrexate administration: a case report and review of literature.

Dai MS, Ho CL, Chen YC, Kao WY, Chao TY.

Department of Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, Republic of China.

Acute Respiratory distress syndrome (ARDS) is a rare complication following intrathecal (IT) injection of methotrexate (MTX) in adult acute lymphoblastic

leukemia (ALL) patients. A 19-year-old man with ALL developed strikingly acute respiratory failure during central nervous system (CNS) prophylaxis with IT MTX administration and cranial irradiation. Histopathologic study of the lungs revealed a pattern of diffuse alveolar damage with interstitial cellular infiltration. His symptoms were relieved soon following treatment with corticosteroids and the pulmonary infiltrates resolved gradually. Pulmonary symptoms did not recur as he was continuously treated with oral corticosteroids.

Publication Types:

- Review
- Review of reported cases

PMID: 11195008 [PubMed - indexed for MEDLINE]

Leukemia 2000 Dec;14(12):2323-4

Intrathecal mitozantrone has to be prohibited.

Dalle JH, Lambilliotte A, Defachelles AS, Mazingue F, Nelken B.

Publication Types:

- Letter

PMID: 11187924 [PubMed - indexed for MEDLINE]

J Pharmacol Exp Ther 2001 Mar;296(3):756-61

Coadministration of intrathecal strychnine and bicuculline effects synergistic allodynia in the rat: an isobolographic analysis.

Loomis CW, Khandwala H, Osmond G, Hefferan MP.

School of Pharmacy, Faculty of Medicine, Memorial University of Newfoundland St. John's, Newfoundland, Canada. cwloomis@morgan.ucs.mun.ca

Tactile allodynia can be modeled in experimental animals by acutely blocking spinal glycine or GABA(A) receptors with intrathecal (i.t.) strychnine (STR) or bicuculline (BIC), respectively. To test the hypothesis that glycine and

GABA effect cooperative (supra-additive) inhibition of touch-evoked responses in the spinal cord, male Sprague-Dawley rats, fitted with chronic i.t. catheters, were used. Following i.t. STR, BIC, or STR + BIC, hair deflection evoked cardiovascular (increased blood pressure and heart rate), motor (scratching, kicking and rippling of the affected dermatomes), and cortical encephalographic responses. Hair deflection was without effect in i.t. saline-treated rats. Isobolographic analysis of STR (ED(50) = 25.1-36.9 microg), BIC (ED(50) = 0.5-0.6 microg), and BIC:STR combination (ED(50) = 0.026-0.034:2.6-3.4 microg) dose-response curves confirmed a supra-additive interaction between BIC and STR in this model. BIC-allodynia was reproduced by i.t. picrotoxin. Pretreatment with i.t. scopolamine, or i.t. muscarine had no effect. STR-allodynia was dose dependently inhibited by i.t. muscimol but not baclofen. The results of this study indicate that 1) glycine and GABA effect cooperative inhibition of low-threshold mechanical input in the spinal cord of the rat; and 2) BIC-allodynia arises from the blockade of GABA(A) receptors and is unrelated to any secondary anticholinesterase activity. The allodynic state induced by the blockade of glycine or GABA receptors is clearly exacerbated by the removal of both inhibitory systems. Their combined loss after neural injury may explain the exaggerated sensitivity to and subsequent miscoding of tactile information as pain.

PMID: 11181903 [PubMed - indexed for MEDLINE]

Spinal Cord 2000 Dec;38(12):728-32 Related Articles, Books, LinkOut

Intrathecal administration of 4-aminopyridine in chronic spinal injured patients.

Halter JA, Blight AR, Donovan WH, Calvillo O.

Department of Physical Medicine and Rehabilitation, Baylor College of Medicine, Houston, Texas, USA.

STUDY DESIGN: Intrathecal administration of 4-aminopyridine (4-AP) in chronic spinal cord injured (SCI) patients. OBJECTIVE: To determine the safety and effects of intrathecal administration of 4-AP in a small population of chronic SCI patients. SETTING: The post anesthesia care unit of a tertiary care hospital. METHODS: Following animal mode studies to establish dosing safety, six subjects with chronic SCI were examined. In each subject, an intrathecal catheter was placed with the tip as close to the lesion level as possible. 4-AP was infused at 5 microg/h for a period of 4-5 h. Vital signs were recorded and sensory-motor physical examinations and pain questionnaires were administered for 24 h. In two patients, samples of cerebrospinal fluid for analysis were drawn from a second intrathecal catheter. RESULTS: No adverse systemic side effects were noted. One patient showed transient improvement in sensory function; two showed transient increases in spasticity; three showed transient increases in cutaneomuscular reflexes and two showed an apparent small increase in volitional motor control. The

concentration of 4-aminopyridine in the cerebrospinal fluid reached a peak of 163 ng/ml at 4 h in one subject and 122 ng/ml at 5 h in the other subject examined. CONCLUSION: Intrathecal administration of 4-aminopyridine at a rate of 5 microg/h does not appear to cause adverse effects and may modify spinal cord function. This route of administration allows local cerebrospinal fluid concentrations equivalent to those produced by maximum tolerable systemic doses, which require 1000 times more drug substance to be delivered to the subject as a whole. Intrathecal administration offers the potential to focus therapeutic effects to the lesion site while minimizing systemic side effects.

Publication Types:

- Clinical trial
- Randomized controlled trial

PMID: 11175372 [PubMed - indexed for MEDLINE]

Reg Anesth Pain Med 2001 Jan-Feb;26(1):35-40 Related Articles, Books, LinkOut

Reg Anesth Pain Med

Hospital discharge after ambulatory knee arthroscopy: A comparison of epidural 2-chloroprocaine versus lidocaine.

Neal JM, Deck JJ, Kopacz DJ, Lewis MA.

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BACKGROUND AND OBJECTIVES: This prospective, randomized, double-blind study compares the efficacy of epidural 2-chloroprocaine and lidocaine for attaining hospital discharge criteria after ambulatory knee arthroscopy. We hypothesized that 2-chloroprocaine would facilitate earlier discharge than lidocaine. METHODS: American Society of Anesthesiologists (ASA) I and II patients were randomized to receive equipotent doses of epidural 3% 2-chloroprocaine or 1.5% lidocaine, both without epinephrine. Time to block resolution and discharge were compared between groups, along with the need for epidural reinjection, surgical times, and postoperative back pain. RESULTS: Twenty-seven patients completed the study, 13 in the 2-chloroprocaine group and 14 in the lidocaine group. The 2-chloroprocaine group was ready for discharge significantly earlier than the lidocaine group (130 17 min [range, 105 to 160] v 191 32 min [range 144 to 251]; P <.0001, 90% power). The lidocaine group required more epidural reinjections. Anesthesia-related side effects were similar in both groups. CONCLUSIONS: Epidural 3% 2-chloroprocaine without epinephrine is an advantageous choice for ambulatory knee arthroscopy. It enables readiness for discharge an hour sooner than 1.5% lidocaine, requires fewer reinjection interventions, and may reduce delayed discharge secondary to prolonged time to void. This clinical

study shows the superiority of epidural 3% 2-chloroprocaine over 1.5% lidocaine for expediting hospital discharge after ambulatory surgery.

Publication Types:

- Clinical trial
- Randomized controlled trial

PMID: 11172509 [PubMed - indexed for MEDLINE]

Exp Neurol 2001 Mar;168(1):144-54 Related Articles, Books, LinkOut

Effects of interleukin-10 (IL-10) on pain behavior and gene expression following excitotoxic spinal cord injury in the rat.

Plunkett JA, Yu CG, Easton JM, Bethea JR, Yezierski RP.

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Intraspinal injection of quisqualic acid (QUIS) produces excitotoxic injury with pathophysiological characteristics similar to those associated with ischemic and traumatic spinal cord injury (SCI). Responses to QUIS-induced injury include an inflammatory component, as well as the development of spontaneous and evoked pain behaviors. We hypothesized that QUIS-induced inflammation and subsequent gene expression contribute to the development and progression of pain-related behaviors and that blockade of inflammation-related gene expression leads to the amelioration of these behaviors. Using the QUIS model of spinal cord injury, we examined whether interleukin-10 (IL-10), a potent anti-inflammatory cytokine, is able to reduce mRNA levels of inflammatory and cell death-related genes leading to a reduction of pain behaviors. The results demonstrate that animals receiving systemic injection of IL-10, 30 minutes following QUIS-induced SCI, showed a significant delay in the onset of excessive grooming behavior, a significant reduction in grooming severity, and a significant reduction in the longitudinal extent of a pattern of neuronal loss within the spinal cord characterized as "grooming-type damage." QUIS injections also resulted in an increase in mRNA levels of interleukin-1 beta (IL-1 beta), cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), CD95 ligand (CD95-L, also called FAS-L/APO-1L), and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). Results of QUIS injury plus IL-10 treatment resulted in a significant downregulation of IL1-beta and iNOS mRNA and these results were supported by Western blot analysis of protein levels following IL-10 treatment. These data suggest that IL-10 reduces inflammation and that targeting injury-induced inflammation is an effective strategy for limiting the extent of neuronal damage following excitotoxic SCI and thus the onset and progression of injury-induced pain

behaviors. Copyright 2001 Academic Press.

PMID: 11170729 [PubMed - indexed for MEDLINE]

Anaesthesia 2001 Jan;56(1):54-60 Related Articles, Books, LinkOut

High-dose intrathecal diamorphine for analgesia after Caesarean section.

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Forty women undergoing elective Caesarean section under spinal anaesthesia using hyperbaric 0.5% bupivacaine were randomly allocated to receive either 0.5 mg or 1 mg intrathecal diamorphine. All women received diclofenac 100 mg at the end of surgery and morphine via a patient-controlled analgesia system. Oral analgesics were not used. Postoperative analgesia was more prolonged and more reliable in the 1-mg group. Mean time to first analgesia was 10.2 h in the 1-mg group and 6.9 h in the 0.5-mg group, and 45% in the 1-mg group used no morphine, compared with 10% in the 0.5-mg group. Mean morphine consumption over 24 h was 5.2 mg in the 1-mg group and 10.6 mg in the 0.5-mg group. Pain scores all tended to be lower in the 1-mg group but this was only significant at 4 h. There were no serious side-effects. Minor side-effects were common but well tolerated, and the incidence did not differ between the groups. If intrathecal diamorphine is used in combination with rectal diclofenac and without oral analgesia, then 1 mg provides superior analgesia to 0.5 mg without any worsening of the side-effects.

Publication Types:

- Clinical trial
- Randomized controlled trial

PMID: 11167437 [PubMed - indexed for MEDLINE]

Br J Cancer 2001 Jan;84(2):157-63 Related Articles, Books, LinkOut

Intrathecal treatment of neoplastic meningitis due to breast cancer with a slow-release formulation of cytarabine.

Jaeckle KA, Phuphanich S, Bent MJ, Aiken R, Batchelor T, Campbell T,

Fulton D, Gilbert M, Heros D, Rogers L, O'Day SJ, Akerley W, Allen J, Baidas S, Gertler SZ, Greenberg HS, LaFollette S, Lesser G, Mason W, Recht L, Wong E, Chamberlain MC, Cohn A, Glantz MJ, Gutheil JC, Maria B, Moots P, New P, Russell C, Shapiro W, Swinnen L, Howell SB.

Department of Medicine, University of California, San Diego, La Jolla, CA 92093, USA.

DepoCyte is a slow-release formulation of cytarabine designed for intrathecal administration. The goal of this multi-centre cohort study was to determine the safety and efficacy of DepoCyte for the intrathecal treatment of neoplastic meningitis due to breast cancer. DepoCyte 50 mg was injected once every 2 weeks for one month of induction therapy; responding patients were treated with an additional 3 months of consolidation therapy. All patients had metastatic breast cancer and a positive CSF cytology or neurologic findings characteristic of neoplastic meningitis. The median number of DepoCyte doses was 3, and 85% of patients completed the planned 1 month induction. Median follow up is currently 19 months. The primary endpoint was response, defined as conversion of the CSF cytology from positive to negative at all sites known to be positive, and the absence of neurologic progression at the time the cytologic conversion was documented. The response rate among the 43 evaluable patients was 28% (CI 95%: 14-41%); the intent-to-treat response rate was 21% (CI 95%: 12-34%). Median time to neurologic progression was 49 days (range 1-515(+)); median survival was 88 days (range 1-515(+)), and 1 year survival is projected to be 19%. The major adverse events were headache and arachnoiditis. When drug-related, these were largely of low grade, transient and reversible. Headache occurred on 11% of cycles; 90% were grade 1 or 2. Arachnoiditis occurred on 19% of cycles; 88% were grade 1 or 2. DepoCyte demonstrated activity in neoplastic meningitis due to breast cancer that is comparable to results reported with conventional intrathecal agents. However, this activity was achieved with one fourth as many intrathecal injections as typically required in conventional therapy. The every 2 week dose schedule is a major advantage for both patients and physicians.

Publication Types:

- Clinical trial
- Multicenter study

PMID: 11161370 [PubMed - indexed for MEDLINE]

J Pharmacol Exp Ther 2001 Feb;296(2):501-9 Related Articles, Books, LinkOut

Effects of A-134974, a novel adenosine kinase inhibitor, on

carrageenan-induced inflammatory hyperalgesia and locomotor activity in rats: evaluation of the sites of action.

McGaraughty S, Chu KL, Wismer CT, Mikusa J, Zhu CZ, Cowart M, Kowaluk EA, Jarvis MF.

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The present study investigated 1) antihyperalgesic actions of a novel and selective adenosine kinase (AK) inhibitor, A-134974 (IC(50) = 60 pM), in the carrageenan model of thermal hyperalgesia; 2) effects of A-134974 on locomotor activity; and 3) relative contributions of supraspinal, spinal, and peripheral sites to the actions of A-134974. Systemic A-134974 (i.p.) dose dependently reduced hyperalgesia (ED(50) = 1 micromol/kg) and at higher doses, reduced locomotor activity (ED(50) = 16 micromol/kg). Administration of A-134974 intrathecally (i.t.) was more potent (ED(50) = 6 nmol) at producing antihyperalgesia than delivering the compound by intracerebralventricular (ED(50) = 100 nmol, i.c.v.) or intraplantar (ED(50) >300 nmol) routes. In contrast, i.c.v. administration of A-134974 was more effective in reducing locomotor activity than i.t. administration (ED(50) values were 1 and >100 nmol, respectively). Increasing the pretreatment time for i.t.-delivered A-134974 caused a greater reduction in locomotor activity (ED(50) = 10 nmol). This was due to diffusion of A-134974 (i.t.) to supraspinal sites. The antihyperalgesic effects of systemic A-134974 were antagonized by the adenosine receptor antagonist theophylline (THEO, 30-500 nmol) administered i.t., but not i.c.v. In the locomotor assay, i.t.-injected THEO did not antagonize hypomobility caused by systemic or i.t. administration of A-134974. However, i.c.v. infusion of THEO did block the hypomotive actions of i.c.v.-, i.t.-, and i.p.-administered A-134974. These data demonstrate that the novel AK inhibitor A-134974 potently reduces thermal hyperalgesia primarily through interactions with spinal sites, whereas its ability to depress locomotor activity is predominantly mediated by supraspinal sites.

PMID: 11160637 [PubMed - indexed for MEDLINE]

Anesthesiology 2000 Apr;92(4):1126-31 Related Articles, Books, LinkOut

Antiallodynic effect of intrathecal gabapentin and its interaction with clonidine in a rat model of postoperative pain.

Cheng JK, Pan HL, Eisenach JC.

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BACKGROUND: Systemic administration of gabapentin was shown previously to attenuate mechanical allodynia in a rat model of postoperative

pain. Because intrathecal administration of gabapentin is effective in other hypersensitivity states, the authors tested its effect in the postoperative model, its interaction with another antiallodynic agent (clonidine), and a possible mechanism of gabapentin action (entry into sites of action via an L-amino acid transporter). METHODS: Male Sprague-Dawley rats were anesthetized with halothane, and an incision of the plantaris muscle of right hind paw induced punctate mechanical allodynia. Withdrawal threshold to von Frey filament application near the incision site was determined before and 2 h after surgery. Then, an intrathecal injection was performed and thresholds were determined every 30 min for 3 h thereafter. RESULTS: Paw incision induced a mechanical hypersensitivity (mechanical threshold > 25 g before incision and < 5 g after). Intrathecal gabapentin dose-dependently (10-100 microg) reduced mechanical allodynia. Intrathecal injection of an inhibitor of L-amino acid transporters or a competitor for this transporter, L-leucine, did not reverse the intrathecal effect of gabapentin. The ED50 of intrathecal gabapentin, clonidine, and their combination were 51, 31, and 9 microg, respectively, and isobolographic analysis showed synergy between gabapentin and clonidine. CONCLUSIONS: Intrathecal gabapentin is effective against tactile allodynia that occurs after paw incision, and interacts synergistically with clonidine. Unlike results in vitro, gabapentin does not obligatorily need to enter cells via the L-amino acid transporter mechanism to achieve its effects in vivo.

PMID: 10754633 [PubMed - indexed for MEDLINE]

Anesthesiology 2000 Apr;92(4):1082-92

Attenuation of ascending nociceptive signals to the rostroventromedial medulla induced by a novel alpha2-adrenoceptor agonist, MPV-2426, following intrathecal application in neuropathic rats.

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BACKGROUND: In the current study, the potency and spread of the antinociception induced by MPV-2426, a novel alpha2-adrenoceptor agonist, was characterized in neuropathic and non-neuropathic animals. METHODS: Neuropathy was induced by unilateral ligation of two spinal nerves in the rat. After lumbar intrathecal or systemic administration of MPV-2426, thermally and mechanically evoked responses of nociceptive neurons of the rostroventromedial medulla were recorded during pentobarbitone anesthesia. To obtain a behavioral correlate of neurophysiologic findings, nocifensor reflex responses evoked by thermal and mechanical stimuli were assessed in unanesthetized neuropathic and control animals. RESULTS: After intrathecal

administration, MPV-2426 and dexmedetomidine produced a dose-related antinociceptive effect, independent of the submodality of the noxious test stimulus or the pathophysiologic condition. This antinociceptive effect was spatially restricted to the inputs from the lower half of the body, and it was reversed by atipamezole, an alpha2-adrenoceptor antagonist. After systemic administration in non-neuropathic animals, MPV-2426 had no antinociceptive effect on responses to rostroventromedial medulla neurons, whereas systemically administered dexmedetomidine produced a dose-related suppression of nociceptive signals to the rostroventromedial medulla, independent of the site of test stimulation. In a behavioral study, intrathecal MPV-2426 produced a dose-dependent suppression of nocifensor responses evoked by noxious mechanical or heat stimuli, whereas systemic administration of MPV-2426 had no effects. CONCLUSIONS: Intrathecal MPV-2426 has spatially limited antinociceptive properties in neuropathic and non-neuropathic conditions because of its action on spinal alpha2-adrenoceptors. These properties may be advantageous when designing therapy for spatially restricted pain problems.

PMID: 10754629 [PubMed - indexed for MEDLINE]

Clin J Pain 2000 Dec;16(4):310-3 Related Articles, Books

Successful treatment of erythromelalgia with intrathecal hydromorphone and clonidine.

Macres S, Richeimer S.

Department of Anesthesiology, University of California, Sacramento 95817, USA.

OBJECTIVE: The objective of this study was to determine if intractable pain from erythromelalgia could be successfully treated with intrathecal hydromorphone and clonidine. DESIGN: A single case of pain from erythromelalgia refractory to multiple treatment modalities was examined and treated. SETTING: The setting is an outpatient pain clinic at a major university teaching hospital. PATIENT: Our patient is an 82-year-old woman with hypertension and peripheral vascular disease. INTERVENTION: Intrathecal opioid and an alpha2-agonist were administered. OUTCOME MEASURES: Outcome was determined by means of patient self-report during office follow-up visits. RESULTS AND CONCLUSIONS: Administration of intrathecal opioid and an alpha2-agonist can be effective in the treatment of the pain of erythromelalgia and offers an alternative pain treatment modality for patients with unremitting pain refractory to more conservative therapy.

PMID: 11153786 [PubMed - indexed for MEDLINE]

Vet J 2001 Jan;161(1):98-9 Related Articles, Books, LinkOut

Comparison of extradural injections of lignocaine and xylazine in azaperone-sedated pigs.

Adetunji A, Ajao AO.

Department of Veterinary Surgery and Reproduction, University of Ibadan, Ibadan, Nigeria.

PMID: 11145835 [PubMed - indexed for MEDLINE]

Nervenarzt 2000 Dec;71(12):1007-11 Related Articles, Books, LinkOut

Comment on:

- Nervenarzt. 2000 Dec;71(12):927-8

[Optimized therapy of spastic syndrome by combination intrathecal baclofen with botulinum toxin].

[Article in German]

Vogt T, Urban PP.

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Intrathecal administration of baclofen has proved to be an effective treatment of spasticity related to CNS damage. Especially patients with spinal spasticity due to traumatic spinal cord injury or transverse myelitis showed a dramatic reduction of spasticity and improvement of their Ashworth scores. The results are, however, often disappointing in patients with muscular hypertension of the extensor muscles, which is frequently found in patients with multiple sclerosis or cerebral hypoxia. In the latter, using intrathecal baclofen may be restricted by serious side effects. Botulinumtoxin A is widely used in patients with various forms of dystonia. It has also been studied in spastic disorders, where local injections were valuable in relieving focal spasticity in hemiparetic patients and in infantile cerebral palsy. It is used only cautiously in severe paraspasticity. The case reports of 4 patients with incomplete and complete paraparesis due to spinal cord injury, neurodegenerative pyramidal disorder, and cerebral hypoxia demonstrate that a combination of intrathecal

baclofen and botulinumtoxin A can improve clinical benefits and reduce side effects.

Publication Types:

- Comment

PMID: 11139983 [PubMed - indexed for MEDLINE]

J Cardiothorac Vasc Anesth 2000 Dec;14(6):639-44 Related Articles, Books, LinkOut

Effect of subarachnoid morphine administration on extubation time after coronary artery bypass graft surgery.

Alhashemi JA, Sharpe MD, Harris CL, Sherman V, Boyd D.

London Health Sciences Centre University of Western Ontario, Canada.

OBJECTIVE: To determine the effects of 2 low doses of intrathecal morphine on extubation time and on postoperative analgesic requirements after coronary artery bypass graft (CABG) surgery. DESIGN: A prospective, randomized, double-blind, placebo-controlled study. SETTING: Tertiary-care university hospital. PARTICIPANTS: Fifty adult patients scheduled for elective primary CABG surgery. INTERVENTIONS: Patients were randomized to receive placebo, 250 microg, or 500 microg intrathecal morphine, preoperatively. Intraoperative fentanyl and midazolam were limited to 15 microg/kg and 20 microg/kg intravenously. Patients were extubated in the intensive care unit by a blinded observer using predefined extubation criteria. MEASUREMENTS AND MAIN RESULTS: Time to extubation and postoperative requirements for morphine, midazolam, nitroglycerin, and sodium nitroprusside were recorded by a blinded observer. Extubation times were 441 207 minutes versus 325 188 minutes versus 409 245 minutes for the placebo, 250-microg, and 500-microg groups ($p = 0.27$). Postoperative morphine requirements in the 250-microg and 500-microg groups were 13.6 7.8 mg and 11.7 7.4 mg, compared with 21.3 6.2 mg in the placebo group ($p = 0.001$). There were no differences among the study groups with regard to postoperative midazolam, nitroglycerin, and sodium nitroprusside requirements. CONCLUSIONS: Despite decreased postoperative morphine requirements, intrathecal morphine administration did not have a clinically relevant effect on extubation time after CABG surgery. This study suggests that 250 microg is the optimal dose of intrathecal morphine to provide significant postoperative analgesia without delaying tracheal extubation.

Publication Types:

- Clinical trial

- Randomized controlled trial

PMID: 11139101 [PubMed - indexed for MEDLINE]

Eur J Pharmacol 2001 Jan 5;411(1-2):93-106 Related Articles, Books, LinkOut

Effects of intravenous and intrathecal sufentanil on a C-fibre reflex elicited by a wide range of stimulus intensities in the rat.

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A C-fibre reflex elicited by electrical stimulation within the territory of the sural nerve was recorded from the ipsilateral biceps femoris muscle in anaesthetised, intact rats, and in anaesthetised rats whose brains had been transected at the level of the obex. The temporal evolution of the response was studied by recording recruitment curves built with stimulus intensities from 0 to 10 times threshold. Both i.v. and i.t. sufentanil resulted in dose-dependent depressions of the reflex. Increasing the stimulus intensity from 1.5 to 10 times threshold resulted in an increase in the ED(50) from 0.58 (0.40-0.86) to 2.40 (1.87-3.31) microgram/kg for i.v. sufentanil and from 0.64 (0.46-0.79) to 1.63 (1.29-3.31) microgram/kg for i.t. sufentanil. With increasing stimulus intensity, the dose-response curves showed a progressive shift to the right, but this shift was only slight with the highest intensity stimuli. The ratios for the ED(50)s for i.v. to i.t. sufentanil were near 1. Following i.v. administration, sufentanil also facilitated the C-fibre reflex and produced tonic inter-stimulus discharges. They disappeared after the i.v. injection of naloxone. In the obex-transected rats, the depressive effect of sufentanil increased, while the facilitations and tonic inter-stimulus discharges disappeared. These findings suggest that the analgesic effects of i.v. ant i.t. sufentanil are similar, probably because sufentanil is highly soluble in lipids. Sufentanil-induced facilitations relate to supraspinal actions on motor controls and/or on the descending control of nociceptive transmission.

PMID: 11137863 [PubMed - indexed for MEDLINE]

Anesth Analg 2001 Jan;92(1):239-43 Related Articles, Books, LinkOut

The combined effects of N-type calcium channel blockers and

morphine on A delta versus C fiber mediated nociception.

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Intrathecal mu opiates produce analgesia presynaptically by inhibiting calcium ion influx and postsynaptically by increasing potassium flux. Mu receptors are expressed on presynaptic terminals of unmyelinated (C), but not myelinated (A delta) nociceptors. Thus, mu-opioids such as morphine may act presynaptically to inhibit C, but not A delta, neurotransmission, and postsynaptically on dorsal horn cells that receive input from A delta and/or C fiber nociceptors. N-type calcium ion channel blockers, such as omega-conotoxin GVIA (omega-CTX), produce analgesia by impeding flux of calcium ions into A delta and C fiber nociceptor terminals. Thus, morphine and omega-CTX attenuated C fiber nociception additively, possibly indicating the same presynaptic site of action. Conversely, morphine and omega- CTX were supraadditively analgesic on an A delta test, indicating that these agents probably have different sites of action. We conclude that although intrathecal application of either morphine or omega-CTX attenuates both A delta and C fiber mediated nociception in rats, the combined effects are quite different for the two fiber types. Specifically, although coadministration of morphine with omega-CTX produces an additive, apparently presynaptic antinociception for C fiber-mediated responses, the combination produces a clearly supraadditive, and likely synergistic effect on A delta mediated nociception, probably by acting at pre and postsynaptic sites, respectively. Implications: This study demonstrates that combined spinal administration of mu opioids and N-type calcium channel blockers may be useful in providing analgesia for A delta mediated (first, sharp) pain while minimizing the side effects of both drugs.

PMID: 11133635 [PubMed - indexed for MEDLINE]

Anesth Analg 2001 Jan;92(1):228-32 Related Articles, Books, LinkOut

The effect of dexamethasone on postoperative pain and emesis after intrathecal neostigmine.

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We evaluated the effect of a single dose of dexamethasone on the incidence and severity of postoperative nausea and vomiting (PONV) after intrathecal injection of tetracaine plus neostigmine. Sixty ASA physical status I patients scheduled for inguinal herniorrhaphy were studied with a randomized, double-

blinded, placebo-controlled protocol. The dexamethasone group (Group D) received 10 mg of dexamethasone IV before performance of spinal anesthesia, whereas the placebo group (Group P) received saline. Spinal anesthesia was performed with intrathecal injection of 15 mg tetracaine plus neostigmine 100 microg in both groups. Pain, PONV, and other side effects were evaluated 24 h after surgery. The duration and severity of analgesia and the incidence of PONV were not significantly different between the two groups. Our results demonstrate that a single dose of dexamethasone (10 mg) did not potentiate the analgesic effect or reduce the incidence of PONV after intrathecal injection of tetracaine and neostigmine. Implications: The results of our evaluation of the effect of IV dexamethasone versus saline control on analgesia and nausea and vomiting after intrathecal neostigmine and tetracaine suggest that IV dexamethasone did not enhance the analgesic effect of neostigmine or reduce the incidence of emesis after intrathecal administration.

Publication Types:

- Clinical trial
- Randomized controlled trial

PMID: 11133633 [PubMed - indexed for MEDLINE]

J Neurooncol 2000 Aug;49(1):41-7 Related Articles, Books, LinkOut

Intrathecal chemotherapy with MX2 for treating glioma dissemination in vivo.

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We examined whether the intrathecal MX2 chemotherapy for treating dissemination of malignant glioma would be a feasible therapy. In the toxicity study, physiological and histological neurotoxicity was not observed in the rats treated with less than 100 microg/kg of MX2 administered intracisternally. But physiological side effects were observed in the treatment group of more than 200 microg/kg and histological brain toxicity was in the treatment group of more than 1000 microg/kg. Dissemination models were induced in rats by intracisternal inoculation of C6 glioma cells. The median survival times of the rats treated with 100 microg/kg of intrathecal MX2 on day 1, 3, or 7 after tumor inoculation were prolonged by 52.4% ($p = 0.0006$), 31.5% ($p = 0.0007$), and 7.1% ($p = 0.0180$), respectively, compared to that of untreated control animals. Intrathecal MX2 treatment also cured 33.6% of rats in the treatment group. These findings suggested that there was a possibility that intrathecal MX2 would be a safe and effective method for treating

dissemination of malignant glioma.

PMID: 11131985 [PubMed - indexed for MEDLINE]

Pain 2000 Oct;88(1):15-22

Spinal effect of the cholecystokinin-B receptor antagonist CI-988 on hyperalgesia, allodynia and morphine-induced analgesia in diabetic and mononeuropathic rats.

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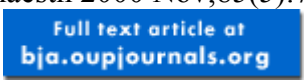
Since evidence points to the involvement of cholecystokinin (CCK) in nociception, we examined the effect of intrathecal CI-988, an antagonist of the CCK-B receptors, on mechanical hyperalgesia and allodynia in normal, mononeuropathic and diabetic rats,. Owing to the anti-opioid activity of CCK, it has been suggested that hyperactivity in the spinal CCK system is responsible for the low sensitivity of neuropathic pain to opioids. We therefore also evaluated the effect of the combination of i.t. CI-988 + i.v. morphine on mechanical hyperalgesia in diabetic and mononeuropathic rats using isobolographic analysis. Although ineffective in normal rats, CI-988 induced antinociceptive effects in diabetic (290 +/- 20 g with a cut-off of 750 g) and mononeuropathic (117 +/- 16 g; cut-off 750 g) rats, suggesting an involvement of the CCKergic system in neurogenic pain conditions. The combination of CI-988 and morphine showed a superadditive interaction in the diabetic rats only (477 +/- 16 g; cut-off 750 g), in comparison with the antinociceptive effect of each drug. In addition, CI-988 exhibited a weak anti-allodynic effect in mononeuropathic rats, and no anti-allodynic effect in diabetic rats. These results show the CCK-B receptor blockade-mediated antinociceptive effects and reveals the antinociceptive action of morphine in diabetic rats after CCKergic system inhibition.

PMID: 11098095 [PubMed - indexed for MEDLINE]

Br J Anaesth 2000 Nov;85(5):747-51



Intrathecal cyclooxygenase inhibitor administration attenuates morphine antinociceptive tolerance in rats.

Wong CS, Hsu MM, Chou R, Chou YY, Tung CS.

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Several lines of evidence suggest that the N-methyl-D-aspartate receptor (NMDA) and nitric oxide (NO) systems are involved in morphine tolerance. Cyclooxygenase (COX) inhibitors may also play a role in morphine tolerance by interacting with both systems. In the present study, we examined the effects of the COX inhibitors N-(2-cyclohexyloxy-4-nitrophenyl) methanesulphonamide (NS-398, selective COX2 inhibitor) and indomethacin (non-selective COX inhibitor) on the development of antinociceptive tolerance of morphine in a rat spinal model. The antinociceptive effect was determined by the tail-flick test. Tolerance was induced by injection of morphine 50 micrograms intrathecally (i.t.) twice daily for 5 days. The effects of NS-398 and indomethacin on morphine antinociceptive tolerance were examined after administering these drugs i.t. 10 min before each morphine injection. Neither NS-398 nor indomethacin alone produced an antinociception effect at doses up to 40 micrograms. NS-398 and indomethacin did not enhance the antinociceptive effect of morphine in naive and morphine-tolerant rats. However, they shifted the morphine antinociceptive dose-response curve to the left when coadministered with morphine during tolerance induction, and reduced the increase in the ED50 of morphine (dose producing 50% of the maximum response) three- to four-fold. Collectively, these findings and previous studies suggest that COX may be involved in the development of morphine tolerance without directly enhancing its antinociceptive effect.

PMID: 11094592 [PubMed - indexed for MEDLINE]

Exp Brain Res 2000 Oct;134(4):490-6 Related Articles, Books, LinkOut

Masculine copulatory behavior is facilitated by intrathecally administered muscarine.

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Behavioral experiments were conducted to examine the role of the cholinergic receptor-agonist muscarine or its antagonist homatropine on the mating behavior of sexually experienced male rats. Male copulatory behavior was recorded after intrathecally administered saline, muscarine (7.5 microg), or homatropine (25 microg). Changes in copulatory behavior were assessed by the following parameters: intromission latency, intromission frequency,

intercopulatory interval, ejaculation latency, and postejaculatory interval. Intromission frequency, intercopulatory interval, and ejaculation latency were decreased significantly by muscarine. Intrathecal homatropine decreased the number of copulating animals (five out of 13). In the five animals that were able to ejaculate after homatropine, intromission latency, intercopulatory interval, and ejaculation latency increased significantly. The effects of both drugs on locomotion were also tested. Muscarine induced no significant changes in locomotion compared with saline. A significant increase in locomotion was found after homatropine treatment. These results suggest that acetylcholine, acting at spinal-cord muscarinic receptors, may be involved in ejaculation.

PMID: 11081831 [PubMed - indexed for MEDLINE]

Masui 2000 Oct;49(10):1152-4 Related Articles, Books, LinkOut

[Extrapyramidal reactions after epidural droperidol].

[Article in Japanese]

Yotsui H, Matsunaga M, Katori K, Kohno S, Higa K.

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We report two patients who developed extrapyramidal reactions after epidural droperidol given to prevent postoperative nausea and vomiting. The reactions may have been related to interactions of drugs given perioperatively. One patient had been taking amlodipine and amitriptyline preoperatively, capable of causing extrapyramidal reactions, and developed akathisia after 2.5 mg of droperidol given epidurally. The other patient had received 1.5 mg of prophylactic epidural droperidol and 10 mg of metoclopramide for postoperative nausea and vomiting, and developed acute dystonia shortly after 0.5 mg of intravenous droperidol.

PMID: 11075569 [PubMed - indexed for MEDLINE]

Brain Res 2000 Nov 17;883(2):178-83 Related Articles, Books, LinkOut

Continuous intrathecal fluid infusions elevate nerve growth factor levels and prevent functional deficits after spinal cord ischemia.

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Continuous intracerebroventricular or intrathecal infusions of neurotrophic factors have been reported to prevent neuronal degeneration, stimulate axonal sprouting and ameliorate behavioral deficits in various models of CNS injury and aging. In the present study, the ability of intrathecal infusions of recombinant human nerve growth factor (NGF) to reduce functional deficits following spinal cord ischemia was investigated. Adult rabbits underwent intrathecal cannulation and continuous infusions of either 300 microg/ml recombinant human NGF or artificial CSF (vehicle) at a rate of 143 microl/day for 7 days prior to induction of spinal cord ischemia. Continuous infusions were maintained after induction of ischemia. Four days later, both NGF-treated and vehicle-infused subjects showed a significant amelioration of functional motor deficits compared to lesioned, non-infused subjects ($P<0.05$). The average duration of tolerated ischemia increased from 23.41.8 min in lesioned, non-infused subjects to 35.53.1 min in lesioned, artificial CSF-infused subjects and 35.64.7 min in NGF-infused subjects (meanS.E.M.). Significantly elevated NGF protein levels were attained within the spinal cords of both NGF-treated subjects and artificial CSF-infused subjects, although levels were substantially higher in NGF-treated subjects (9.83.8 ng/g in NGF-infused vs. 2.00.4 ng/g in vehicle-infused and only 0.40.2 ng/g in lesioned, non-infused animals). These findings indicate that the process of intrathecal cannulation and fluid infusion elicits alterations in the spinal cord environment that are neuroprotective, including spontaneous elevations in NGF levels.

PMID: 11074046 [PubMed - indexed for MEDLINE]

Cerebrovasc Dis 2000 Nov-Dec;10(6):424-30 Related Articles, Books, LinkOut

Intrathecal administration of thrombin inhibitor ameliorates cerebral vasospasm. Use of a drug delivery system releasing hirudin.

Kudo A, Suzuki M, Kubo Y, Watanabe M, Yoshida K, Doi M, Kuroda K, Ogawa A.

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The role of thrombin as a spasmogen after subarachnoid hemorrhage was evaluated using the intrathecally administered thrombin inhibitor hirudin, released from a drug delivery system (DDS) based on collagen in a canine vasospasm model. The DDS was implanted into the cisterna magna with autologous blood in the hirudin-treated group. The reduction in the

angiographical diameter of the basilar artery was only 19% in the hirudin-treated group on day 7, showing a significant difference between hirudin-treated and nontreated groups ($p < 0.01$). These results suggest that thrombin is an important cause of vasospasm. The collagen DDS has great potential for treatment in the cerebrospinal fluid milieu. Copyright 2000 S. Karger AG, Basel

PMID: 11070371 [PubMed - indexed for MEDLINE]

Eur J Pharmacol 2000 Nov 3;407(3):267-72 Related Articles, Books, LinkOut

Intrathecal Zn2+ attenuates morphine antinociception and the development of acute tolerance.

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Vesicular Zn2+, released in the brain and from small dorsal root ganglion neurons, interacts with opioid as well as N-methyl-D-aspartate (NMDA) receptors. We investigated the effect of Zn2+ on morphine antinociception in mice (tail flick assay), as well as acute tolerance and dependence, phenomena associated with NMDA activity. Administered intrathecally (i.t.), Zn2+ inhibited morphine antinociception in a dose-related fashion. Zn2+ also inhibited acute tolerance to morphine antinociception (5 h after 100 mg/kg of morphine). Injection i.t. of di-sodium calcium ethylenediamine tetra acetic acid (Na+Ca2+ EDTA), a chelator of divalent cations, had no effect on analgesia, acute tolerance or acute dependence. However, withdrawal jumps produced by naloxone (1 mg/kg s.c.) in morphine-pellet implanted mice (3 days) were potentiated by injections twice daily of 10 nmol of Na+Ca2+ EDTA, suggesting that endogenous Zn2+ tends to inhibit long-term development of withdrawal. These data suggest that the availability of Zn2+ is an important factor in opioid activity.

PMID: 11068022 [PubMed - indexed for MEDLINE]

Eur J Pharmacol 2000 Nov 3;407(3):245-55 Related Articles, Books, LinkOut

Neuropeptide FF attenuates allodynia in models of chronic inflammation and neuropathy following intrathecal or

intracerebroventricular administration.

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Experiments were conducted to explore the effects of Neuropeptide FF acting at spinal and supraspinal sites in models of chronic inflammatory or neuropathic pain and of acute pain. Neuropeptide FF was administered intrathecally (i.t.; 10.0, 25.0 and 50.0 nmol) or intracerebroventricularly (i.c.v.; 10.0, 12.5 and 15.0 nmol) either 24 h after inflammation-inducing injections of Freund's Complete Adjuvant in one hind paw or 7 days after unilateral sciatic nerve constriction. Evoked pain was assessed by measuring the withdrawal response threshold (in grams of pressure) to a mechanical stimulus applied to the plantar surface of the injured paw. Neuropeptide FF dose-dependently attenuated the allodynic response (i.e., withdrawal from a normally innocuous stimulus) to mechanical stimulation in the inflammatory and neuropathic model following i.t. (ED50=20.86 nmol and ED50=18.91 nmol, respectively) and i.c.v. (ED50=12.31 nmol and ED50=11.68 nmol, respectively) administration. Pretreatment with naloxone (2.0 mg/kg; s.c.) attenuated the anti-allodynic effect of i.t. or i.c.v. Neuropeptide FF in rats experiencing inflammatory, but not neuropathic pain. In contrast, Neuropeptide FF administered i.t. (10.0, 25.0 and 50.0 nmol) or i.c.v. (10.0, 12.5 and 15.0 nmol) had no effect on the response to acute thermal or mechanical stimulation. Neuropeptide FF injected i.t. or i.c.v. in inflamed or neuropathic rats did not produce any sign of motor dysfunction. These results suggest that Neuropeptide FF acting at spinal and supraspinal sites plays a role in modulating chronic, but not acute pain. Furthermore, the results suggest that the anti-allodynic effect of Neuropeptide FF is mediated indirectly by naloxone-sensitive opioid mechanisms in rats subjected to inflammatory, but not neuropathic pain.

PMID: 11068020 [PubMed - indexed for MEDLINE]

Neurosci Lett 2000 Oct 20;293(1):45-8 Related Articles, Books, LinkOut

Modification of cardiovascular response of adenosine A2 receptor agonist by adenylate cyclase in the spinal cord of rats.

Koh HC, Lee TK, Kang JS, Lee CH, Lee H, Paik DJ, Shin IC.

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This study was performed to investigate the influence of spinal adenosine A2

receptors on the central regulation of blood pressure (BP) and heart rate (HR), and to define whether its mechanism is mediated by adenylate cyclase or guanylate cyclase. Intrathecal (i.t.) administration of drugs at the thoracic level were performed in anesthetized, artificially ventilated male Sprague-Dawley rats. Injection (i.t.) of adenosine A2 receptor agonist, 5'-(N-cyclopropyl)-carboxamidoadenosine (CPCA; 1, 2 and 3 nmol) produced a dose dependent decrease of BP and HR. Pretreatment with adenylate cyclase inhibitor, MDL-12,330, attenuated the depressor and bradycardiac effects of CPCA (2 nmol), but not with guanylate cyclase inhibitor, LY-83,583. These results suggest that adenosine A2 receptor in the spinal cord plays an inhibitory role in the central cardiovascular regulation and that the depressor and bradycardiac actions are mediated by adenylate cyclase.

PMID: 11065134 [PubMed - indexed for MEDLINE]

Expert Opin Investig Drugs 2000 Oct;9(10):2403-10 Related Articles, Books, LinkOut

An evaluation of intrathecal ziconotide for the treatment of chronic pain.

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Ziconotide, the synthetic form of cone snail peptide varpi-conotoxin MVIIA, is a neurone-specific N-type calcium channel blocker with an analgesic and neuroprotective effect. Intrathecal ziconotide has been recommended for approval by the FDA for the management of chronic pain. Spinally administered ziconotide produces analgesia by blocking neurotransmitter release from primary nociceptive afferents and prevents the propagation of pain signals to the brain. It has an advantage over intrathecal morphine in that there is no development of tolerance after prolonged use. Systemic toxicity is considerably reduced by administration of smaller doses intrathecally and selective delivery to the site of action in the nervous system. Nevertheless, there are neurological adverse effects due to delay in clearance of ziconotide from the neural tissues. Overall, ziconotide has a favourable risk/benefit ratio with advantages over several currently available intrathecal therapies for pain.

Publication Types:

- Review
- Review literature

PMID: 11060815 [PubMed - indexed for MEDLINE]

J Neurosci 2000 Nov 1;20(21):8131-7

Antagonism of the melanocortin system reduces cold and mechanical allodynia in mononeuropathic rats.

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The presence of both pro-opiomelanocortin-derived peptides and melanocortin (MC) receptors in nociception-associated areas in the spinal cord suggests that, at the spinal level, the MC system might be involved in nociceptive transmission. In the present study, we demonstrate that a chronic constriction injury (CCI) to the rat sciatic nerve, a lesion that produces neuropathic pain, results in changes in the spinal cord MC system, as shown by an increased binding of (125)I-NDP-MSH to the dorsal horn. Furthermore, we investigated whether intrathecal administration (in the cisterna magna) of selective MC receptor ligands can affect the mechanical and cold allodynia associated with the CCI. Mechanical and cold allodynia were assessed by measuring withdrawal responses of the affected limb to von Frey filaments and withdrawal latencies upon immersion in a 4.5 degrees C water bath, respectively. We show that treatment with the MC receptor antagonist SHU9119 has a profound anti-allodynic effect, suggesting that the endogenous MC system has a tonic effect on nociception. In contrast, administration of the MC4 receptor agonists MTII and d-Tyr-MTII primarily increases the sensitivity to mechanical and cold stimulation. No antinociceptive action was observed after administration of the selective MC3 receptor agonist Nle-gamma-MSH. Together, our data suggest that the spinal cord MC system is involved in neuropathic pain and that the effects of MC receptor ligands on the responses to painful stimuli are exerted through the MC4 receptor. In conclusion, antagonism of the spinal melanocortin system might provide a new approach in the treatment of neuropathic pain.

PMID: 11050135 [PubMed - indexed for MEDLINE]

J Neurosci 2000 Nov 1;20(21):8061-8

Regeneration of lesioned corticospinal tract fibers in the adult rat induced by a recombinant, humanized IN-1 antibody fragment.

Brosamle C, Huber AB, Fiedler M, Skerra A, Schwab ME.

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Axons in the CNS of higher vertebrates generally fail to regenerate after injury. This lack of regeneration is crucially influenced by neurite growth inhibitory protein constituents of CNS myelin. We have shown previously that a monoclonal antibody (mAb IN-1) capable of binding and neutralizing Nogo-A, a myelin-associated inhibitor of neurite growth, can induce long-distance axonal regeneration and increased structural plasticity with improved functional recovery in rat models of CNS injury. In this paper we demonstrate that a partially humanized, recombinant Fab fragment (rIN-1 Fab) derived from the original mAb IN-1, was able to promote long-distance regeneration of injured axons in the spinal cord of adult rats. When infused into a spinal cord injury site, regrowth of corticospinal fibers in 11 of 18 animals was observed after a survival time of 2 weeks. Regenerating fibers grew for >9 mm beyond the lesion site and arborized profusely in the distal cord. Regenerated fibers formed terminal arbors with varicosities in the spinal cord gray matter, strongly resembling synaptic points of contact to neurons in the spinal cord distal to the lesion. In animals that had received a bovine serum albumin solution or a recombinant IN-1 fragment that had been mutated in the antigen binding site (mutIN-1 Fab), no significant growth beyond normal lesion-induced sprouting was observed. Neutralization of endogenous nerve growth inhibitors represents a novel use of recombinant antibody technology with potential therapeutic applications after traumatic CNS lesions.

PMID: 11050127 [PubMed - indexed for MEDLINE]

Neuropharmacology 2000 Oct;39(13):2785-91

The antinociceptive effects of alpha7 nicotinic agonists in an acute pain model.

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Nicotinic receptors have been found to play a role in modulating pain transmission in the CNS. Activation of cholinergic pathways by nicotine and nicotinic agonists has been shown to elicit antinociceptive effects in a variety of species and pain tests. The involvement of alpha(7) nicotinic receptors in nicotinic analgesia was assessed after spinal (i.t.) and intraventricular (i.c.v.)

administration in mice. Dose-dependent antinociceptive effects were seen with the alpha(7) agonist choline after spinal and supraspinal injection using the tail-flick test. Furthermore, alpha(7) antagonists MLA and alpha-BGTX significantly blocked the effects of choline. Dihydro-beta-erythroidine and mecamylamine failed to block choline-induced antinociception. These results strongly support the involvement of alpha(7) subunits in choline's antinociceptive effects. DMXB and 4-OH-DMXB, partial alpha(7) agonists, failed to elicit a significant antinociceptive effect. However, they blocked choline-induced antinociception in a dose-dependent manner following i.t. injection. This antagonism is probably related to their partial agonistic properties of the alpha(7) receptors. These studies suggest that activation of alpha(7) receptors in the CNS elicits antinociceptive effects in an acute thermal pain model.

PMID: 11044748 [PubMed - indexed for MEDLINE]

J Infect 2000 Jul;41(1):95-7 Related Articles, Books, LinkOut

Treatment of a vancomycin-resistant Enterococcus faecium ventricular drain infection with quinupristin/dalfopristin and review of the literature.

Tan TY, Pitman I, Penrose-Stevens A, Simpson BA, Flanagan PG.

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Central nervous system infections involving vancomycin-resistant Enterococcus faecium (VREF) are infrequently described and pose significant therapeutic difficulties, because these organisms are intrinsically resistant to many antibiotics. We describe the use of intrathecal quinupristin/dalfopristin to treat a VREF-associated infection in a neuro--surgical patient.

PMID: 11041712 [PubMed - indexed for MEDLINE]

Brain Res 2000 Oct 20;881(1):1-8 Related Articles, Books, LinkOut

Differential antagonism of endomorphin-1 and endomorphin-2 spinal antinociception by naloxonazine and 3-methoxynaltrexone.

Sakurada S, Hayashi T, Yuhki M, Fujimura T, Murayama K, Yonezawa A, Sakurada C, Takeshita M, Zadina JE, Kastin AJ, Sakurada T.

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To determine the role of spinal mu-opioid receptor subtypes in antinociception induced by intrathecal (i.t.) injection of endomorphin-1 and -2, we assessed the effects of beta-funaltrexamine (a selective mu-opioid receptor antagonist) naloxonazine (a selective antagonist at the mu(1)-opioid receptor) and a novel receptor antagonist (3-methoxynaltrexone) using the paw-withdrawal test. Antinociception of i.t. endomorphins and [D-Ala(2), MePhe(4), Gly(ol)(5)]enkephalin (DAMGO) was completely reversed by pretreatment with beta-funaltrexamine (40 mg/kg s.c.). Pretreatment with a variety of doses of i.t. or s.c. naloxonazine 24 h before testing antagonized the antinociception of endomorphin-1, -2 and DAMGO. Judging from the ID(50) values of naloxonazine, the antinociceptive effect of endomorphin-2 was more sensitive to naloxonazine than that of endomorphin-1 or DAMGO. The selective morphine-6beta-glucuronide antagonist, 3-methoxynaltrexone, which blocked endomorphin-2-induced antinociception at each dose (0.25 mg/kg s.c. or 2.5 ng i.t.) that was inactive against DAMGO, did not affect endomorphin-1-induced antinociception but shifted the dose-response curve of endomorphin-2 3-fold to the right. These findings may be interpreted as indicative of the existence of a novel mu-opioid receptor subtype in spinal sites, where antinociception of morphine-6beta-glucuronide and endomorphin-2 are antagonized by 3-methoxynaltrexone. The present results suggest that endomorphin-1 and endomorphin-2 may produce antinociception through different subtypes of mu-opioid receptor.

PMID: 11033087 [PubMed - indexed for MEDLINE]

Anesthesiology 2000 Oct;93(4):976-80 Related Articles, Books, LinkOut

Analgesic effects of caudal and intramuscular S(+)-ketamine in children.

Koinig H, Marhofer P, Krenn CG, Klimscha W, Wildling E, Erlacher W, Nikolic A, Turnheim K, Semsroth M.

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BACKGROUND: Previous studies suggest that caudal administration of ketamine cause effective analgesia. The purpose of the current study was to compare the clinical effectiveness and plasma concentrations of S(+)-ketamine after caudal or intramuscular administration in children to distinguish between local and systemic analgesia. METHODS: After induction of general anesthesia, 42 patients, aged 1 to 7 yr, scheduled to undergo inguinal hernia repair randomly received a caudal (caudal group) or intramuscular (intramuscular group) injection of 1 mg/kg S(+)-ketamine. Intraoperatively, heart rate (HR), mean arterial pressure (MAP) and arterial oxygen saturation

were measured. Postoperative measurements included duration of analgesia, a four-point sedation score, and hemodynamic and respiratory monitoring for 6 h in the recovery room. Analgesic requirements in the recovery room were assessed by an independent blinded observer using an observational pain/discomfort scale (OPS). Plasma samples for determination of ketamine concentrations were obtained before and 10, 20, 30, 45, 60, 90, 120, and 180 min after injection of S(+)-ketamine. RESULTS: A significantly longer duration of analgesia ($P < 0.001$) was observed after caudal administration (528 min [220-1,440 min]; median [range]) when compared with intramuscular administration (108 min [62-1,440 min]) of S(+)-ketamine. Plasma levels of ketamine were significantly lower from 10 to 45 min after caudal administration than after intramuscular injection. CONCLUSION: Caudal S(+)-ketamine provides good intra- and postoperative analgesia in children. Despite similar plasma concentrations during most of the postoperative observation period, caudal S(+)-ketamine provided more effective analgesia than did intramuscular S(+)-ketamine, indicating a local analgesic effect.

Publication Types:

- Clinical trial
- Randomized controlled trial

PMID: 11020749 [PubMed - indexed for MEDLINE]

Rev Esp Anestesiol Reanim 2000 Aug-Sep;47(7):323-4 Related Articles, Books, LinkOut

Full text at Revista Española de Anestesiología y Reanimación

[Accidental epidural administration of potassium chloride].

[Article in Spanish]

Bermejo-Alvarez MA, Cosio F, Hevia A, Iglesias-Fernandez C.

Publication Types:

- Letter

PMID: 11002718 [PubMed - indexed for MEDLINE]

Neurosci Lett 2000 Sep 29;292(1):25-8 Related Articles, Books, LinkOut

Regulation of the development of allodynia by intrathecally administered P2 purinoceptor agonists and antagonists in mice.

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Effects of agonists and antagonists of P2X-purinoceptors on the regulation of the development of allodynia were examined in mice; the drugs were administered intrathecally to the spinal cord. Suramin (5, 10 microg) and pyridoxalphosphate-6-azophenyl-2', 4'-disulfonic acid (PPADS), antagonists of P2X receptors, inhibited prostaglandin (PG) E(2)-induced allodynia. PPADS did not block glutamate-induced allodynia. alpha,beta-Methylene ATP (alpha, beta-meATP), an agonist of P2X receptor, elicited allodynia. alpha, beta-me ATP-induced allodynia was blocked by co-administration of alpha,beta-meATP with PPADS, MK 801 or N(omega)-nitro-L-arginine methyl ester (L-NAME). Suramin at higher doses (20, 40 microg) induced allodynia, which was inhibited by MK 801 or L-NAME. These results suggest that ATP P2X receptors in the spinal cord are involved in the regulation of tactile allodynia. Glutamate receptor and nitric oxide systems play an important role in the development of allodynia produced by alpha,beta-meATP and suramin.

PMID: 10996441 [PubMed - indexed for MEDLINE]

J Neurosci 2000 Sep 15;20(18):7074-9 Related Articles, Books, LinkOut

Dynorphin promotes abnormal pain and spinal opioid antinociceptive tolerance.

Vanderah TW, Gardell LR, Burgess SE, Ibrahim M, Dogrul A, Zhong CM, Zhang ET, Malan TP Jr, Ossipov MH, Lai J, Porreca F.

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The nonopioid actions of spinal dynorphin may promote aspects of abnormal pain after nerve injury. Mechanistic similarities have been suggested between opioid tolerance and neuropathic pain. Here, the hypothesis that spinal dynorphin might mediate effects of sustained spinal opioids was explored. Possible abnormal pain and spinal antinociceptive tolerance were evaluated after intrathecal administration of [D-Ala(2), N-Me-Phe(4), Gly-

ol(5)]enkephalin (DAMGO), an opioid mu agonist. Rats infused with DAMGO, but not saline, demonstrated tactile allodynia and thermal hyperalgesia of the hindpaws (during the DAMGO infusion) and a decrease in antinociceptive potency and efficacy of spinal opioids (tolerance), signs also characteristic of nerve injury. Spinal DAMGO elicited an increase in lumbar dynorphin content and a decrease in the mu receptor immunoreactivity in the spinal dorsal horn, signs also seen in the postnerve-injury state. Intrathecal administration of dynorphin A(1-17) antiserum blocked tactile allodynia and reversed thermal hyperalgesia to above baseline levels (i.e., antinociception). Spinal dynorphin antiserum, but not control serum, also reestablished the antinociceptive potency and efficacy of spinal morphine. Neither dynorphin antiserum nor control serum administration altered baseline non-noxious or noxious thresholds or affected the intrathecal morphine antinociceptive response in saline-infused rats. These data suggest that spinal dynorphin promotes abnormal pain and acts to reduce the antinociceptive efficacy of spinal opioids (i.e., tolerance). The data also identify a possible mechanism for previously unexplained clinical observations and offer a novel approach for the development of strategies that could improve the long-term use of opioids for pain.

PMID: 10995854 [PubMed - indexed for MEDLINE]

Natl Med J India 1998 Sep-Oct;11(5):209-12

A randomized double-blind sham-controlled study of intrathecal human anti-tetanus immunoglobulin in the management of tetanus.

Agarwal M, Thomas K, Peter JV, Jeyaseelan L, Cherian AM.

Department of Gastroenterology, Christian Medical College, Tamil Nadu, India.

BACKGROUND: Tetanus is a major cause of mortality and morbidity in developing countries. Various modalities of treatment to prevent progression of the disease and alter its outcome have been tried. This study was designed to evaluate the role of intrathecal human anti-tetanus immunoglobulin (TIG) in the management of tetanus. METHODS: Thirty-six adult patients presenting to an university-affiliated teaching hospital were stratified based on the severity of disease into mild and severe disease, and subsequently randomly allocated to receive either 250 i.u. of TIG intrathecally or a sham procedure mimicking the lumbar puncture. RESULTS: In mild tetanus, TIG administration significantly retarded the rate of progression ($p = 0.05$), reduced the duration of hospital ($p = 0.01$) and intensive care unit stay ($p = 0.05$), need for tracheostomies ($p = 0.03$) and the dose of sedatives required for control of spasms ($p = 0.01$). In mild tetanus, the mortality rates were 20%

and 30% in the treated and control groups, respectively. CONCLUSION: We suggest that TIG is useful in reducing the morbidity, progression of disease and mortality in patients presenting with mild tetanus.

Publication Types:

- Clinical trial
- Randomized controlled trial

PMID: 10997166 [PubMed - indexed for MEDLINE]

J Pharmacol Exp Ther 2000 Oct;295(1):291-4

Discovery of "self-synergistic" spinal/supraspinal antinociception produced by acetaminophen (paracetamol).

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The mechanism of the analgesic action of one of the world's most widely used drugs-acetaminophen (paracetamol)-remains largely unknown more than 100 years after its original synthesis. Based on the present findings, this elusiveness appears to have resulted from experimental strategies that concentrated on a single target site or mechanism. Here we report on the use of analyses that we previously developed to investigate possible brain/spinal-cord site-site interaction in acetaminophen-induced antinociception. Spinal (intrathecal) administration of acetaminophen to mice produced dose-related, naloxone-insensitive antinociception with an ED(50) value of 137 (S.E. = 23) microgram = 907 (S.E. =153) nmol. In contrast, supraspinal (i.c.v.) acetaminophen administration had no effect. However, combined administration of acetaminophen in fixed ratios to brain and spinal cord produced synergistic antinociception, ED(50) = 57 (S.E. = 9) microgram, that reverted toward additivity, ED(50) = 129 (S.E. = 23) microgram, when the opioid antagonist naloxone was given spinally (3.6 microgram = 10 nmol) or s.c. (3.6 mg/kg). These findings demonstrate for the first time that acetaminophen-induced antinociception involves a "self-synergistic" interaction between spinal and supraspinal sites and, furthermore, that the self-synergy involves an endogenous opioid pathway.

PMID: 10991992 [PubMed - indexed for MEDLINE]

Sheng Li Xue Bao 1998 Feb;50(1):43-8

[Effect of intrathecal injection of dopamine receptor agonists/antagonists on pain and acupuncture analgesia in rats].

[Article in Chinese]

Gao X, Xin BM, Zhu CB, Wu GC, Xu SF.

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Some selective dopamine receptor agonists and antagonists were tested on rat tail flick model to investigate the role of D1 and D2 dopamine receptor in pain and acupuncture analgesia (AA). It was found that intrathecal administration (i.t.) of D2 receptor agonist LY171555 or D1/D2 receptor agonist apomorphine increased pain threshold and had a potentiating effect on AA. In contrast, D1 receptor agonist SKF38393 had no effect. It D1 receptor antagonist SCH23390 or D2 receptor antagonist sulpiride attenuated the effect of AA. The results suggest that D2 receptor is involved in pain modulation and activation of D2 receptor and enhances AA in the spinal cord, while such effect is absent in D1 receptor and inactivation of D1 receptor attenuates AA.

PMID: 11324516 [PubMed - indexed for MEDLINE]

Acta Anaesthesiol Scand 2000 Sep;44(8):940-5

Onset and offset of intrathecal morphine versus nalbuphine for postoperative pain relief after total hip replacement.

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BACKGROUND: We designed this study to compare the postoperative analgesic effects of intrathecal morphine and nalbuphine, the endpoints being onset and offset of action. METHODS: Geriatric patients scheduled for elective total hip replacement under continuous spinal anaesthesia were randomized to two double-blinded groups in the recovery room as soon as they experienced a pain score higher than 3 cm on the visual analogue scale (VAS, 0-10 cm). Either 160 microg morphine or 400 microg nalbuphine in 4 ml normal saline were administered intrathecally. Pain scores on VAS, rescue analgesia (diclofenac and morphine, not allowed during the first 60 min), and the adverse effects (respiratory depression, postoperative nausea and vomiting, itching) were recorded for 24 h after surgery. RESULTS: The study was stopped after inclusion of 2 x 12 patients due to slow onset of analgesia in the

morphine patients. In the nalbuphine group, when compared to the morphine group, the time to a pain score <3 cm (86 vs. 3132 min, P<0.001), the time to the lowest pain score (1811 vs. 6675 min, P<0.001) and the time to the first systemic analgesic intervention for a pain score >3 cm (218256 vs. 1076440 min, P<0.05) were significantly shorter. The analgesic requirements during the first 24 h were significantly lower in the morphine group (P<0.001). CONCLUSION: We conclude that after total hip replacement, administration of intrathecal nalbuphine resulted in a significantly faster onset of pain relief and shorter duration of analgesia than intrathecal morphine.

Publication Types:

- Clinical trial
- Randomized controlled trial

PMID: 10981570 [PubMed - indexed for MEDLINE]

Neuroreport 2000 Aug 21;11(12):2817-9 Related Articles, Books

Spinal anandamide inhibits nociceptive transmission via cannabinoid receptor activation in vivo.

Harris J, Drew LJ, Chapman V.

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The endocannabinoid anandamide has affinity for cannabinoid and vanilloid receptors, which have opposing effects on nociceptive transmission. Effects of spinal administration of anandamide on innocuous and noxious evoked spinal neuronal responses in non-inflamed and carrageenin-inflamed rats were studied. Anandamide (0.1-50 microg/50 microl) had inconsistent effects in non-inflamed rats. Following carrageenin inflammation, anandamide (50 microg/50 microl) significantly reduced evoked neuronal responses, C-fibre mediated non-potentiated and post-discharge responses of neurones reduced to 65 5% and 57 10% of control, respectively. Effects of anandamide were blocked by SR141716A, a selective CB1 receptor antagonist. Spinal SR141716A (0.001-1 ng/50 microl) alone did not influence neuronal responses in inflamed rats. Spinal anandamide inhibited nociceptive transmission via CB1 receptors; following inflammation there is evidence for a loss of spinal endogenous cannabinoid tone.

PMID: 10976969 [PubMed - indexed for MEDLINE]

Stroke 2000 Sep;31(9):2141-8 Related Articles, Books, LinkOut

Microcatheter intrathecal urokinase infusion into cisterna magna

for prevention of cerebral vasospasm: preliminary report.

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BACKGROUND AND PURPOSE: The feasibility of preventing vasospasm by intrathecal anterograde infusion of urokinase (UK) into the cisterna magna was studied in patients with recently ruptured aneurysms who had just undergone the placement of a Guglielmi detachable coil (GDC). METHODS: Immediately after complete embolization with the use of GDC-10 coils, 15 patients with Hunt and Hess neurological grades III and IV received 60 000 IU of UK in normal saline through a microcatheter advanced into the cisterna magna. UK infusion was repeated once or twice over a period of 2 to 3 days according to a decision based on CT evidence of a subarachnoid clot remaining in the cisterns. Before administering the last UK infusion, we obtained CT confirmation of almost complete clearance of clots in the basal cisterns. RESULTS: In all 15 patients, the microcatheter was advanced easily into the cisterna magna by use of the over-the-wire microcatheter technique. In 8 patients who received thrombolytic therapy within 24 hours of the ictus, there was almost complete clearance of the clot in the basal cisterns within 2 days of suffering the insult. When UK was injected at 24 to 48 hours after the insult, 7 patients manifested CT evidence of clearance at the latest 4 days after suffering the insult. In all 15 patients, CT scans obtained within 24 hours of the final UK administration showed complete resolution of clots in the basal cistern and almost complete resolution of clots in the basal interhemispheric fissure and bilateral proximal sylvian fissures. Although one patient developed a transient neurological deficit, no patients manifested permanent delayed neurological deficits as a result of vasospasm. Outcome assessment according to the Glasgow Outcome Scale, no less than 3 months after GDC placement, revealed good recovery in all patients, and none developed hydrocephalus requiring a shunt procedure. CONCLUSIONS: In patients with recently ruptured aneurysms, GDC placement followed by immediate intrathecal administration of UK from the cisterna magna may be a safe and reasonable means of preventing vasospasms and may result in improved treatment outcomes.

Publication Types:

- Clinical trial

PMID: 10978043 [PubMed - indexed for MEDLINE]

Acta Anaesthesiol Scand 2000 Aug;44(7):868-72 Related Articles, Books, LinkOut

Intrathecal adenosine administration in abdominal hysterectomy

lacks analgesic effect.

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BACKGROUND: Adenosine (Ado) is known, from studies in both animals and humans, to produce antinociception when administered systemically or intrathecally (IT). The current aim was to evaluate, in a placebo-controlled, randomised, double-blind study, whether IT adenosine given before surgery could reduce anaesthetic requirement and the need of opioids during 48 h after visceral surgery. METHOD: Forty women (37-66 years, ASA I and II) scheduled for elective hysterectomy were included. Before inducing the standardised O2/N2O/isoflurane/fentanyl anaesthesia, the patients received an IT injection of either adenosine (500 microg in 1 ml volume) or placebo 1 ml (saline). Intraoperative anaesthetic drug doses and haemodynamics were recorded. Postoperative pain was assessed by visual analogue scale. For postoperative analgesia, cetobemidone was provided via intravenous patient-controlled analgesia (PCA). RESULTS: During surgery, there were no differences between groups in anaesthetic requirement or haemodynamic parameters. Postoperative cetobemidone requirements were similar in both groups (median 48 mg for adenosine/50 mg for saline) during the first 48 postoperative hours. CONCLUSION: IT adenosine did not influence the requirement of anaesthetic drug or postoperative analgesics after hysterectomy.

Publication Types:

- Clinical trial
- Randomized controlled trial

PMID: 10939701 [PubMed - indexed for MEDLINE]

Orv Hetil 2000 May 14;141(20):1091-2 Related Articles, Books

[Anesthesia with injection of cocaine into the spinal canal. 1900].

[Article in Hungarian]

Dollinger Gy.

Publication Types:

- Biography
- Classical article
- Historical article

Personal Name as Subject:

- Dollinger Gy

PMID: 10928909 [PubMed - indexed for MEDLINE]

Brain Res 2000 Jul 28;872(1-2):93-101 Related Articles, Books, LinkOut

Spinal mechanisms underlying A-85380-induced effects on acute thermal pain.

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Systemic administration of nicotinic receptor (nAChR) agonists is antinociceptive in models of acute pain whereas their intrathecal (i. t.) administration has been reported to be antinociceptive, nociceptive or without effect. It has been hypothesized that the action induced is dependent upon the subtype and location of the nAChR activated. In addition, there is considerable evidence that nAChR ligand-induced antinociception is mediated by other neurotransmitter systems via descending pathways from the brainstem to the spinal cord. The present study investigated the effects of i. t. and systemic administration of A-85380, a novel nAChR agonist, in the paw withdrawal model of acute thermal pain in the rat. Given i.t. , A-85380 (1 and 10 nmol/rat) decreased the latency to paw withdrawal by 2-4 s. This pronociception was accompanied by a spontaneous flinching behavior. Both of these effects were differentially blocked by i.t. pretreatment with the nAChR antagonists mecamylamine (10 nmol)>MLA (100 nmol)>DHbetaE (50% with 1000 nmol) but not by alpha-bungarotoxin (0% at 0.63 nmol). Given systemically, A-85380 (0.56 &mgr;mol/kg, i.p.) induced antinociception as indicated by an increased latency to paw withdrawal, an effect differentially altered by i.t. pretreatment with monoaminergic antagonists (100 nmol/rat). While mecamylamine and prazosin had no effect, scopolamine, methysergide and MDL 72222 partially antagonized and idazoxan completely antagonized A-85380-induced antinociception. Finally, as measured by in vivo microdialysis, levels of 5-HT, but not NE, in the i.t. space of the lumber region of the spinal cord were significantly increased following the systemic administration of A-85380. Together these data suggest that the nociceptive properties of spinally administered nAChR agents are not mediated by either an alpha(4)beta(2) or an alpha(7) subtype nAChR, whereas the antinociceptive properties of systemically-administered nAChR agents are mediated by descending noradrenergic, serotonergic and muscarinic inhibitory pathways.

PMID: 10924680 [PubMed - indexed for MEDLINE]

Anesth Analg 2000 Aug;91(2):417-22

The effect of spinal ibuprofen on opioid withdrawal in the rat.

Dunbar SA, Karamov IG, Buerkle H.

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This study examines the effect of spinal ibuprofen on the behavioral manifestations associated with the opioid abstinence syndrome. Rats (n = 8 per group) were infused for 5 days with morphine and then pretreated with a spinal bolus dose of ibuprofen before systemic naloxone antagonism (300 microg). Groups included ibuprofen S(+) 1. 36, 13.6, and 136 nmol, and ibuprofen R(-) 136 nmol. A separate group of saline-infused rats was given ibuprofen S(+) 136 nmol before naloxone antagonism. Ibuprofen S(+), but not R(-), dose-dependently and stereospecifically blocked opioid withdrawal hyperalgesia but did not significantly alter other signs of the opioid abstinence syndrome. We conclude that hyperalgesia associated with opioid withdrawal can be blocked by spinally administered ibuprofen, and suggest that there may be a role for spinal prostaglandins in the enhancement of nociception observed in association with the opioid abstinence syndrome. Implications: This study shows that spinal ibuprofen blocks opioid withdrawal hyperalgesia in the rat in a stereospecific fashion, implicating the likely release of spinal prostaglandins during withdrawal and their possible role as neuromodulators in the enhancement of nociception that accompanies this phenomenon.

PMID: 10910860 [PubMed - indexed for MEDLINE]

: Anesthesiology 2000 Aug;93(2):473-81

Effects of radolmidine, a novel alpha2 -adrenergic agonist compared with dexmedetomidine in different pain models in the rat.

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BACKGROUND: Intrathecally administered alpha2-adrenoceptor agonists produce effective antinociception, but sedation is an important adverse effect. Radolmidine is a novel alpha2-adrenoceptor agonist with a different pharmacokinetic profile compared with the well-researched dexmedetomidine.

This study determined the antinociceptive and sedative effects of radolmidine in different models of acute and chronic pain. Dexmedetomidine and saline served as controls. METHODS: Male Sprague-Dawley rats were studied in acute pain (tail flick), carrageenan inflammation, and the spinal nerve ligation model of neuropathic pain. Mechanical allodynia was assessed with von Frey filaments, cold allodynia with the acetone test, and thermal hyperalgesia with the paw flick test. Locomotor activity-vigilance was assessed in a dark field. Dexmedetomidine and radolmidine were administered intrathecally in doses of 0.25 microg, 2.5 microg, 5 microg, and 10 microg. RESULTS: In the tail flick test, radolmidine showed a dose-dependent antinociceptive effect, being equipotent compared with dexmedetomidine. In carrageenan inflammation, intrathecal doses of 2.5 microg or 5 microg of dexmedetomidine/radolmidine produced significant antinociception compared with saline ($P < 0.01$). The two drugs were equianalgesic. In the neuropathic pain model, an intrathecal dose of 5 microg dexmedetomidine-radolmidine had a significant antiallodynic effect compared with saline ($P < 0.01$). The two drugs were equipotent. Intrathecal administration of both dexmedetomidine and radolmidine dose dependently decreased spontaneous locomotor acitivity-vigilance, but this effect was significantly smaller after intrathecal administration of radolmidine than after intrathecal dexmedetomidine. CONCLUSIONS: Radolmidine and dexmedetomidine had equipotent antinociceptive effects in all tests studied. However, radolmidine caused significantly less sedation than dexmedetomidine, probably because of a different pharmacokinetic profile.

PMID: 10910498 [PubMed - indexed for MEDLINE]

Planta Med 2000 Jun;66(5):412-7 Related Articles, Books

Modulatory role of ginsenosides injected intrathecally or intracerebroventricularly in the production of antinociception induced by kappa-opioid receptor agonist administered intracerebroventricularly in the mouse.

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We examined the effects of ginseng total saponin and several ginsenosides injected intrathecally (i.t.) or intracerebroventricularly (i.c.v.) on the antinociception induced by U50, 488H (trans-3,4-dichloro-N-methyl-N-[2- (1-pyrrolidinyl)cyclohexyl]benzeocetamide; a kappa opioid receptor agonist) administered i.c.v. The tail-flick test was used as an analgesic assay. Total saponin fraction at doses of 0.1 to 20 micrograms, which when administered intrathecally (i.t.) or intracerebroventricularly (i.c.v.) alone did not affect the latencies of tail-flick threshold, attenuated dose-dependently the inhibition of the tail-flick response induced by U50, 488H (60 micrograms) administered i.c.v. The duration of antagonistic action of total saponin fraction against U50, 488H-induced antinociception lasted at least for 6 h. Various doses (from 0.1

to 1 microgram) of ginsenosides Rb1, Rb2, Rc, Rd, and Rg1, but not Re, injected i.t. dose-dependently attenuated antinociception induced by U50, 488H administered i.c.v. Furthermore, various doses (from 1 to 10 micrograms) of ginsenosides Rb2 and Re, but not Rb1, Rc, Rd, and Rg1, injected i.c.v. dose-dependently attenuated antinociception induced by U50, 488H administered i.c.v. In summary, ginsenosides Rb1, Rb2, Rc, Rd, and Rg1 administered spinally appear to be responsible for blocking the antinociception induced by U50, 488H administered supraspinally, whereas ginsenosides Rb2 and Re administered supraspinally appear to be responsible for blocking the antinociception induced by U50, 488H administered supraspinally.

PMID: 10909259 [PubMed - indexed for MEDLINE]

J Ethnopharmacol 2000 Jul;71(1-2):211-8

Antinociceptive mechanisms of dipsacus saponin C administered intrathecally in mice.

Suh H, Song D, Huh S, Son K, Kim Y.

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Dipsacus saponin C (DSC) administered intrathecally (i.t.) showed antinociceptive effect in a dose-dependent (from 3.75 to 30 microg) manner as measured by the tail-flick assay. The antinociception induced by DSC at the dose of 30 microg reached at peak 7.5 min and almost returned to the control level after 60 min. 5-Amino-valeric acid (5-AVA, a GABA(A) receptor antagonist, from 1 to 20 microg) and SR 95531 (a GABA(B) receptor antagonist, from 0.1 to 2 ng) dose-dependently attenuated i.t. administered DSC-induced increase of the inhibition of the tail-flick response. The i.t. injection of yohimbine (an alpha(2)-adrenergic receptor antagonist, from 1 to 20 microg) and methysergide (a serotonin receptor antagonist, from 1 to 20 microg), but not naloxone (from 2 to 8 microg), significantly attenuated inhibition of the tail-flick response induced by DSC (30 microg) administered i.t. Sulfated cholecystokinin (CCK, from 0.05 to 0.5 ng) injected i.t. significantly reduced the inhibition of the tail-flick response induced by DSC (30 microg) administered i.t. Our results suggest that DSC shows an antinociceptive effect when it is administered spinally and GABA(A), GABA(B), alpha(2)-adrenergic and serotonin receptors located at the spinal cord level, but not opioid receptors, may be involved in DSC-induced antinociception. Furthermore, CCK may play an important role for the modulation of i. t. injected DSC-induced antinociception.

PMID: 10904165 [PubMed - indexed for MEDLINE]

Vet Surg 2000 May-Jun;29(3):272-7 Related Articles, Books

The hemodynamic effects of intrathecal oxytocin in normal dogs.

Neath PJ, Brown DC, Hughes D, Perkowski SZ.

Department of Clinical Studies, University of Pennsylvania, School of Veterinary Medicine, Philadelphia 19104-6010, USA.

OBJECTIVE: To evaluate the hemodynamic effects produced by intrathecal administration of oxytocin in healthy isoflurane-anesthetized dogs. STUDY DESIGN: Prospective single-dose trial. ANIMAL POPULATION: Six healthy purpose-bred adult dogs weighing between 7.3 and 14.5 kg. METHODS: Dogs were anesthetized with isoflurane and instrumented. Oxytocin at a dosage of 1.6 microg/kg was administered intrathecally at the cisternal space at time 0. Hemodynamic data were recorded immediately before and at 1, 5, 15, 30, and 60 minutes after oxytocin administration. Statistical analysis included an analysis of variance (ANOVA) for repeated measures over time. A P < .05 was considered significant. RESULTS: Baseline values standard error of the mean for heart rate, mean arterial pressure, central venous pressure, cardiac output, systemic vascular resistance, mean pulmonary arterial pressure, pulmonary arterial occlusion pressure, and pulmonary vascular resistance were 101 11 beats/minute, 76 7 mm Hg, 4 4 mm Hg, 1.9 0.7 L/min, 3834 2556 dynes x sec/cm5, 14 3 mm Hg, 4 2 mm Hg, and 430 201 dynes x sec/cm5, respectively. Variations from the baseline values were seen in all parameters after intrathecal oxytocin administration, but no statistically significant differences were found. CONCLUSION: The intrathecal injection of 1.6 microg/kg of oxytocin is associated with minimal hemodynamic effects during isoflurane anesthesia. CLINICAL RELEVANCE: This study revealed no clinically significant deleterious effects from the intrathecal administration of oxytocin, and investigations into its use as a perioperative analgesic are therefore warranted.

PMID: 10871229 [PubMed - indexed for MEDLINE]

Life Sci 2000;66(23):2239-45 Related Articles, Books

The spinal antinociceptive effect of FR140423 is mediated through kyotorphin receptors.

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Department of Immunology and Inflammation, Medicinal Biology Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan.

We investigated the antinociceptive effect of a novel anti-inflammatory and analgesic drug, 3-(difluoromethyl)-1-(4-methoxyphenyl)-5-[4-(methylsulfinyl)phenyl]pyraz ole (FR140423), in the tail-pinch test in mice,

and evaluated the mechanism of action of FR140423 using L-leucyl-L-arginine (Leu-Arg), a kyotorphin (endogenous Met-enkephalin releaser) receptor antagonist, L-NG-nitroarginine methylester (L-NAME), an inhibitor of nitric oxide (NO) synthase, and methylene blue (MB), an inhibitor of activation of guanylate cyclase. Oral administration of FR140423, at doses of 5-80 mg/kg, produced a dose-dependent antinociceptive effect with an ED50 value of 18 mg/kg. This antinociception was reversed by intrathecal (i.t.) (10 microg/mouse), but not by intracerebroventricular (i.c.v.) (100 microg/mouse), injection of Leu-Arg. Moreover, the antinociceptive effect of i.t. injection of FR140423 with an ED50 value of 3.7 microg/mouse was completely antagonized by co-administered Leu-Arg 10 microg/mouse. However, L-NAME (2000 mg/kg s.c.) and MB (200 mg/kg s.c.) did not antagonize the antinociception of FR140423. These findings suggest that FR140423 plays a role in nociceptive modulation in the spinal cord, being antinociceptive via the kyotorphin-Met-enkephalin pathway but not via the peripheral NO-cyclic GMP pathway.

PMID: 10855944 [PubMed - indexed for MEDLINE]

Neuroscience 2000;98(2):339-44 Related Articles, Books, LinkOut

The effect of intrathecal endomorphin-2 on the flexor reflex in normal, inflamed and axotomized rats: reduced effect in rats with autotomy.

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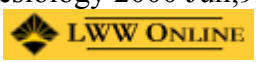
Endomorphin-2, a newly discovered endogenous opioid peptide and agonist at the mu-opioid receptor, was injected intrathecally in normal rats and animals with unilateral peripheral inflammation or sciatic nerve section and its effect on the nociceptive flexor reflex was analysed. In normal rats, intrathecal endomorphin-2 induced a strong and dose-dependent depression of the reflex, which was naloxone-reversible. The effect of intrathecal endomorphin-2 was fairly brief, lasting for about 20-30 min at the highest dose, 4 microg. The effect of endomorphin-2 in inflamed rats was not significantly different from that in normals. After nerve section some rats developed autotomy behavior. In these rats endomorphin-2 had significantly reduced effect. However, the reflex depressive effect of intrathecal endomorphin-2 was unchanged in axotomized rats without autotomy.It is suggested that intrathecal endomorphin-2 has antinociceptive effect in the rat spinal cord under normal and inflammatory conditions. After peripheral nerve injury the sensitivity to endmorphin-2 may be reduced in rats that exhibit ongoing neuropathic pain-like behaviors.

PMID: 10854766 [PubMed - indexed for MEDLINE]

Anesthesiology 2000 Jun;92(6):1740-5



The mechanical antihyperalgesic effect of intrathecally administered MPV-2426, a novel alpha2 -adrenoceptor agonist, in a rat model of postoperative pain.

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BACKGROUND: MPV-2426 is a novel alpha2-adrenoceptor agonist developed for spinal pain therapy. It has proved to be effective in physiologic and neuropathic conditions. In the current study its effectiveness on mechanical hyperalgesia was assessed in a rat model of postoperative pain. METHODS: Rats with intrathecal catheters were anesthetized with pentobarbital, and a 1-cm incision was made in the plantar aspect of the foot and closed. During postoperative days 1 and 2 the antihyperalgesic effects induced by intrathecal MPV-2426, clonidine, and dexmedetomidine were determined by assessing the hind limb withdrawal threshold to calibrated von Frey hairs applied to the skin of the hind paw adjacent to the wound. RESULTS: MPV-2426 administered into the lumbar spinal cord produced a dose-dependent (0.3-10 microg) attenuation of the mechanical hyperalgesia, and this antihyperalgesic effect was completely reversed by yohimbine (1 mg/kg, subcutaneous), an alpha2-adrenoceptor antagonist. Dexmedetomidine (1-3 microg) produced an equipotent antihyperalgesic effect, whereas the effect of clonidine (1-10 microg) was markedly weaker. MPV-2426 (10 microg in 20 microl) administered adjacent to the wound did not produce any effect. Preoperative treatment with an antihyperalgesic dose of MPV-2426 did not prevent the development of hyperalgesia. CONCLUSIONS: Intrathecal MPV-2426 dose-dependently attenuates postoperative hyperalgesia to mechanical stimulation because of an action on alpha2 adrenoceptors. Its antihyperalgesic action is as effective as that produced by dexmedetomidine and is considerably stronger than that produced by clonidine. However, preoperative treatment with MPV-2426 does not prevent the development of postoperative hyperalgesia.

PMID: 10839926 [PubMed - indexed for MEDLINE]

Brain Res 2000 Jun 9;867(1-2):200-9

Medullary and intrathecal injections of 17beta-estradiol in male rats.

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The following experiments were designed to investigate the role of estrogen in central autonomic nuclei on autonomic tone and reflex control of heart rate. Male Sprague-Dawley rats were anesthetized with sodium thiobutabarbital (100 mg/kg) and instrumented to record blood pressure and heart rate. Efferent vagal and renal nerve activities were recorded and used to assess changes in parasympathetic and sympathetic tone, respectively. The cardiac baroreflex was evoked using a single bolus injection of phenylephrine (0.1 mg/kg) both before and following either intrathecal injection of estrogen (0.5 microM; 1 microl) to influence sympathetic preganglionic neurons of the intermediolateral cell column or bilateral injection of estrogen (0.5 microM; 100 nl/side) into the nucleus tractus solitarius, rostral ventrolateral medulla or nucleus ambiguus. The cardiac baroreflex was significantly enhanced following both intrathecal and medullary injections of estrogen. Efferent vagal nerve activity was significantly increased following injection of estrogen into the nucleus tractus solitarius, nucleus ambiguus and the intrathecal space. Renal sympathetic nerve activity was significantly depressed following injection of estrogen into the nucleus tractus solitarius, rostral ventrolateral medulla and the intrathecal space. In all cases, simultaneous injection of estrogen with the selective estrogen receptor antagonist, ICI 182,780 (1 pM) blocked all previously observed changes in baroreflex function and autonomic tone. These results demonstrate a role for estrogen in the reflex control of heart rate and as a central modulator of autonomic tone in male rats.

PMID: 10837814 [PubMed - indexed for MEDLINE]

Zentralbl Veterinarmed A 2000 Mar;47(2):65-72

Analgesic, behavioural and cardiopulmonary effects of epidurally injected medetomidine (Domitor) in goats.

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This study was carried out in order to evaluate the analgesic, sedative, immobilizing and cardiopulmonary effects of medetomidine in goats after lumbosacral epidural injection of three (10, 20 and 30 micrograms/kg body weight) doses. The volume of the injection for all three medetomidine doses was 5 ml in sterile water. Seventeen clinically healthy, Small East African goats of either sex and weighing between 12 and 22 kg (mean SD; 14.8 2.5 kg body weight) were used. The animals were randomly assigned to two groups. Seven goats were used for evaluating analgesic, behavioural and cardiopulmonary effects while 10 were used for experimental surgery. The

cardiopulmonary values and rectal temperature were determined and recorded at time 0 (preinjection) and at 5, 10, 15, 20 and 30 min, and thereafter at 15-min intervals up to 180 min after injection. Analgesia of the flank and perineum was determined at time 0 (preinjection) and at 5, 10, 15, 30, 60, 120 and 180 min using a scoring system. The spread of analgesia to the thorax, neck, forelimbs and head was also determined and recorded. The onset and duration of lateral recumbency was noted and recorded. Medetomidine at the given doses induced variable cardiopulmonary depression, which was not detrimental to the animals. All three doses (10, 20 and 30 micrograms/kg) of medetomidine induced adequate analgesia of the flank and perineum. Analgesia extended to the thorax, forelimbs, neck and head. The duration of lateral recumbency was 136 and 166 min for the 20 and 30 micrograms/kg medetomidine doses, respectively. The duration of lateral recumbency was not determined for the animal given 10 micrograms/kg medetomidine. Signs of sedation (lowering of the head, drooping of the lower lip, partial to complete closure of the eyes and salivation) were noted after administration of all three doses. It can be concluded from this study that all three doses induced adequate analgesia of the flank and perineum. Surgical analgesia of the flank of goats was achieved after lumbosacral epidural administration of 20 micrograms medetomidine/kg, diluted in 5 ml of sterile water. Surgery was not performed with the other doses (10 and 30 micrograms/kg) of medetomidine.

PMID: 10803105 [PubMed - indexed for MEDLINE]

Eur J Anaesthesiol 2000 Jan;17(1):69-70 Related Articles, Books, LinkOut

Accidental injection of thiopental into the epidural space.

Weigert A, Lawton G.

Publication Types:

- Letter

PMID: 10798894 [PubMed - indexed for MEDLINE]

Stroke 2000 May;31(5):1195-7 Related Articles, Books, LinkOut

Comment on:

- Stroke. 1999 Jul;30(7):1409-16

Intrathecal sodium nitroprusside improves cerebral blood flow

and oxygenation in refractory cerebral vasospasm and ischemia in humans.

Vajkoczy P, Hubner U, Horn P, Bauhuf C, Thome C, Schilling L, Schmiedek P, Quintel M, Thomas JE.

Publication Types:

- Comment
- Letter

PMID: 10797186 [PubMed - indexed for MEDLINE]

Zhongguo Yao Li Xue Bao 1999 Aug;20(8):737-40 Related Articles, Books

Intrathecal injection of corticotropin inhibited nitric-oxide synthase-positive neuron increase in rat spinal cord after formalin-induced hyperalgesia.

Zhou HJ, Li HD, Li XC, Ruan HZ, Zhao BY.

Department of Physiology, Third Military Medical University, Chongqing, China.

AIM: To study the effects of corticotropin (Cor) on formalin-induced hyperalgesia and the change of nitric-oxide synthase (NOS)-positive neurons in spinal dorsal horn in rats. METHODS: Measurement of pain intensity rating (PIR), NADPH-d histochemistry, and Fos immunohistochemistry were adopted. RESULTS: The increases of NOS-positive neurons, Fos, NOS/Fos double labelling neurons of the spinal dorsal horn and the PIR after formalin injection were markedly inhibited by intrathecal injecting (ith) Cor (0.5-1.5 U), which were obviously attenuated by L-arginine (Arg, 5-15 nmol, ith), the substrate of NOS. CONCLUSION: Cor inhibits formalin-induced hyperalgesia by the decrease of NOS-positive neurons in the spinal dorsal horn of rats.

PMID: 10678109 [PubMed - indexed for MEDLINE]

J Clin Oncol 2000 May;18(9):2003-4 Related Articles, Books, LinkOut

Comment on:

- J Clin Oncol. 1999 Oct;17(10):3110-6

Intrathecal cytarabine and bone marrow suppression.

Barista I.

Publication Types:

- Comment
- Letter

PMID: 10784644 [PubMed - indexed for MEDLINE]

Anesthesiology 2000 May;92(5):1350-60 Related Articles, Books, LinkOut

Spinal tonicaine: potency and differential blockade of sensory and motor functions.

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BACKGROUND: Long-acting local anesthetics are beneficial for the management of postoperative pain and chronic pain. The authors recently reported that a single injection of N-beta-phenylethyl-lidocaine (tonicaine), a quaternary lidocaine derivative, effectively blocks rat sciatic nerve function four to nine times longer than lidocaine, with a predominance of sensory versusmotor blockade. The purposes of this study were to measure directly the potency of this charged drug by internal perfusion of cultured neuronal cells, and to evaluate the differential blockade of sensory versus motor function via spinal route in rats. METHODS: The tonic and additional use-dependent blockade of Na+ currents by internal tonicaine was assayed in cultured GH3 cells during whole cell voltage-clamp conditions. In addition, tonicaine was injected into the intrathecal space of rats at intervertebral space L4-L5, and the proprioceptive, motor, and sensory functions, and tissue integrity, subsequently were evaluated. RESULTS: Internal application of tonicaine in GH3 cells revealed that it was approximately 80 times more potent in blocking Na+ currents than was externally applied lidocaine. In vivotesting in a rat neuraxial anesthesia model showed that tonicaine at 0.5 mm produced blockade that lasted much longer than that produced by bupivacaine even at approximately a 55 times higher concentration (28.8 mm). Tonicaine spinal block also produced a longer duration of sensory than motor blockade (112.5 +/- 16.3 min vs. 45.8 +/- 7.1 min). Evidence of neurotoxicity was seen at a concentration of 1.0 mm. CONCLUSION: In vitro testing shows that tonicaine displays a higher affinity for the local anesthetic binding site than does lidocaine; in vivotesting indicates that tonicaine elicits sensory blockade of a duration significantly longer than that elicited by bupivacaine. Tonicaine, however, has a narrow therapeutic index, with substantial neurotoxicity at 1 mm in rats, and may have limited clinical value.

PMID: 10781281 [PubMed - indexed for MEDLINE]

Pain 2000 May;86(1-2):55-61

Intrathecally administered spermine produces the scratching, biting and licking behaviour in mice.

Tan-No K, Taira A, Wako K, Niijima F, Nakagawasai O, Tadano T, Sakurada C, Sakurada T, Kisara K.

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Intrathecal (i.t.) administration of spermine (0.1-10000 fmol), an endogenous polyamine, produced the behavioural response mainly consisting of biting and/or licking of the hindpaw along with a slight hindlimb scratching directed toward the flank in mice, which peaked at 5-15 min and almost disappeared at 30 min after an injection. The behaviour induced by spermine (10 pmol) was dose-dependently inhibited by intraperitoneal injection of morphine (0.125-0.5 mg/kg). The characteristic behaviour was also inhibited dose-dependently by i.t. co-administration of ifenprodil (62.5-4000 pmol), a competitive antagonist of the polyamine recognition site on N-methyl-D-aspartate (NMDA) receptor ion-channel complex, and D(-)-2-amino-5-phosphonovaleric acid (D-APV) (0.5-2 nmol) and 3-((+/-)-2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid (CPP) (7. 8-500 pmol), the competitive NMDA receptor antagonists, and (5R, 10S)-(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,b]cycloheptene-5, 10-imine hydrogen maleate (MK-801) (0.5-4 nmol), an NMDA ion-channel blocker, but not by 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX), a non-NMDA receptor antagonist. Both (2S, 3S)-[cis-2-(diphenylmethyl)-N-[(2-methoxyphenyl)-methyl]-1-azabicy clo [2.2.2]octane-3-amine] (CP-96,345), a non-peptidic neurokinin-1 (NK-1) receptor antagonist, and CP-96,344, its inactive 2R,3R enantiomer, inhibited spermine-induced behavioural response in a dose-dependent manner. However, [Tyr(6), D-Phe(7), D-His(9)]-substance P(6-11) (sendide) and [D-Phe(7), D-His(9)]-substance P(6-11), the selective antagonists for NK-1 receptors, were without affecting spermine-induced behaviour. These results indicate that spermine-induced behaviour is mediated through the polyamine recognition site on NMDA receptor ion-channel complex without the involvement of substance P system in the mouse spinal cord.

PMID: 10779660 [PubMed - indexed for MEDLINE]

J Neurooncol 1999;45(2):175-83

Clinical trial of intrathecal administration of 5-fluoro-2'-deoxyuridine for treatment of meningeal dissemination of

malignant tumors.

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Intrathecal administration of 5-fluoro-2'-deoxyuridine (FdUrd) was performed in patients with meningeal dissemination of malignant tumors during the period from January 1996 to September 1998, and they were followed up until February 1999. The study population consisted of 23 patients: 12 with lung cancer, 4 with breast cancer, 2 with colon cancer, 1 with malignant lymphoma, 2 with glioblastoma and 2 with metastatic brain tumors of unknown origin. FdUrd was administered intrathecally through an Ommaya reservoir placed in the lateral ventricle initially at a dose of 1 microg twice per week, and the dose was increased to 10 microg and administration schedule was also increased every day. Headache and nuchal pain were relieved in all patients regardless of responsiveness to intrathecal FdUrd therapy as determined from the findings in the cerebrospinal fluid (CSF). Patients showed no side effects during the course of intrathecal chemotherapy except for slight nausea in two patients and dull headache in one. Sixteen of the 23 patients showed decreased cell number in the cerebrospinal fluid (CSF). Positive cytological findings in CSF became negative in 6 of the 23 patients, and the levels of CSF tumor markers were decreased in 14. Responsiveness to intrathecal administration of FdUrd was defined as 'response' when both the cell number and tumor markers were decreased in both ventricular and spinal CSF or when the cell number was decreased in cases in which the tumor markers were not detected. Overall, 16 of the 23 patients (70%) showed complete or partial responses to intrathecal FdUrd therapy as determined from CSF findings. These results demonstrated the efficacy of intrathecal FdUrd chemotherapy without apparent neurotoxicity for treatment of meningeal dissemination of malignant tumors.

Publication Types:

- Clinical trial
- Clinical trial, phase i
- Clinical trial, phase ii

PMID: 10778733 [PubMed - indexed for MEDLINE]

Neurol Res 2000 Mar;22(2):160-4 Related Articles, Books, LinkOut

Long-term intrathecal administration of glycine prevents mechanical hyperalgesia in a rat model of neuropathic pain.

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Neuropathic pain has been postulated to be mediated, in part, by amino acid neurotransmitters including glycine. The current study examined the effects of continuous intrathecal glycine administration (0.1 mumol 0.5 microliter-1 h-1) on the development of mechanical hyperalgesia and other features of neuropathic pain evoked by unilateral loose ligation of the sciatic nerve in the rat. Each hind paw was tested for withdrawal threshold to mechanical stimuli prior to, and after ligation at intervals of 3, 6, 9, 12 and 16 days. Pain behavior (posture and gait) and hind paw dystrophic features (redness and swelling) were also examined. Glycine increased the normal mechano-nociceptive responses and prevented the development of mechano-nociceptive hyperalgesia. Spontaneous nociceptive behavior and hind paw dystrophic features, seen in the saline treated rats, were significantly diminished. Our results suggest that spinal cord inhibitory glycinergic activity is important for normal mechano-receptive responsitivity and development of mechano-nociceptive hyperalgesia in this model.

PMID: 10763503 [PubMed - indexed for MEDLINE]

J Neurooncol 1999;44(3):233-41 Related Articles, Books, LinkOut

Intrathecal busulfan treatment of human neoplastic meningitis in athymic nude rats.

Archer GE, Sampson JH, McLendon RE, Friedman AH, Colvin OM, Rose M, Sands H, McCullough W, Fuchs HE, Bigner DD, Friedman HS.

Department of Pathology, Duke University Medical Center, Durham, NC 27710, USA.

The current study was designed to evaluate the toxicity and activity of Spartaject Busulfan, a microcrystalline preparation of busulfan, following its intrathecal administration into a nude rat model of human neoplastic meningitis. Animals were treated through permanent indwelling subarachnoid catheters. Human glioma D-456 MG growing in the subarachnoid space was treated with 8.1 micromol of intrathecal Spartaject Busulfan. Single-dose therapy was also subsequently compared with 4 doses of 8.1 and 2.0 micromol busulfan, respectively, against D-456 MG neoplastic meningitis. Additional experiments evaluated a saline control versus 8.1 micromol x 1, 6.2 micromol x 4 and 4.1 micromol x 4, respectively, against D-456 MG. A single dose of 8.1 micromol of intrathecal Spartaject Busulfan resulted in an increase in median survival of 61.7% compared with the saline control. In experiment 2, all busulfan treatments showed increases in median survival of 142.8% (8.1 micromol x 1), 52.3% (2.0 micromol x 4), and 23% (8.1 micromol x 4) ($p < 0.001$ for all groups) compared with the saline control. These results suggest that a narrow therapeutic dose range for both toxicity and activity has been defined for intrathecal busulfan in the treatment of human neoplastic

meningitis in athymic nude rats. Although busulfan has only limited activity against solid tumors, the high doses achievable in the CSF following intrathecal administration coupled with the steep dose-response relationships of alkylating agents, provide rationale for further evaluation of this agent.

PMID: 10720203 [PubMed - indexed for MEDLINE]

Brain Res 2000 Feb 21;856(1-2):281-90

Comparison of cytosine arabinoside delivery to rat brain by intravenous, intrathecal, intraventricular and intraparenchymal routes of administration.

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We evaluated the delivery of 14C-cytosine arabinoside (AraC) to rat brain by: 1) intravenous (IV) bolus, by 2) intrathecal (IT) and 3) intraventricular (IVT) infusion, and by 4) convection-enhanced delivery (CED) into the caudate nucleus. Plasma and brain AraC metabolites were measured with HPLC, and distribution and concentration of 14C-AraC in brain sections were measured by quantitative autoradiography. After IV administration, the alpha and beta plasma half-lives were 1.9 and 46.5 min, respectively. The blood-to-brain transfer constant of AraC was 2.51.4 microliter g(-1) min(-1), compatible with high water solubility. After IT and IVT administration, tissue levels were high at the brain and ventricular surfaces, but declined exponentially into brain. After CED, maximum brain levels were up to 10,000 times higher than the IV group, and the distribution pattern was one of high 14C-AraC concentration in the convective component, with exponentially declining concentrations outside this region. The rate loss constant from brain was 0.0020.0004 min(-1), suggesting that AraC was accumulating in brain cells. AraC was metabolized into uracil arabinoside within the brain. 14C-AraC was infused into 1 dog and distributed widely in the ipsilateral hemisphere. These studies suggest that delivery of AraC to brain parenchyma by the IV, IT or IVT routes will be subtherapeutic. Delivery by CED can achieve, and maintain, therapeutic levels of AraC in the brain, and should be further evaluated as a potential method of drug delivery.

PMID: 10677637 [PubMed - indexed for MEDLINE]

Br J Pharmacol 2000 Jan;129(2):351-9

Effects of spinally administered P2X receptor agonists and

antagonists on the responses of dorsal horn neurones recorded in normal, carrageenan-inflamed and neuropathic rats.

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1. The function and role of P2X receptors in the spinal transmission of nociception was investigated using the selective P2X receptor agonists, alpha,beta-methylene ATP (alpha,beta-me ATP) and beta, gamma-methylene-L-ATP (beta,gamma-me-L-ATP) and the P2X receptor antagonists pyridoxal-phosphate-6-azophenyl-2',4'-disulphonate (PPADS) and suramin. 2. Intrathecal administration of 5 and 50 microg of beta,gamma-me-L-ATP produced a significant facilitation of the C-fibre evoked response and a tendency towards increased excitability of the post-discharge, but not Abeta-fibre evoked response of dorsal horn neurones recorded in normal animals. Administration of similar doses of alpha,beta-me ATP did not produce an overall change in the response of the neuronal population. 3. Peripheral administration of 20 microg of these agonists into the paw of the rat evoked firing in the dorsal horn neurones. 4. Intrathecal administration of the antagonists, suramin (50 and 500 microg) and PPADS (5, 50 and 500 microg), to normal animals and to animals with a model of neuropathy induced by spinal nerve ligation did not alter the evoked neuronal responses. In contrast, intrathecal administration of 500 microg of suramin to animals 3 h after the induction of carrageenan inflammation produced a significant inhibition of the C-fibre evoked response of the neurones. Similar inhibitions were also seen following high doses of intrathecal PPADS, although this did not reach significance. 5. These results suggest that spinal P2X receptors may play a role in the modulation of spinal nociceptive transmission following the development of inflammation, but that these receptors play at most a minor role in spinal nociceptive processing in normal and neuropathic animals.

PMID: 10694242 [PubMed - indexed for MEDLINE]

Pain 2000 Mar;85(1-2):59-64 Related Articles, Books, LinkOut

Intrathecal lithium reduces neuropathic pain responses in a rat model of peripheral neuropathy.

Shimizu T, Shibata M, Wakisaka S, Inoue T, Mashimo T, Yoshiya I.

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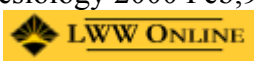
We tested the ability of lithium (Li(+)) to block heat hyperalgesia, cold allodynia, mechanical allodynia and mechanical hyperalgesia in rats experimentally subjected to painful peripheral neuropathy. Chronic

constrictive injury (CCI) to the sciatic nerve induced persistent hyperalgesia and allodynia. Intrathecal injection of Li(+) (2.5-40 micromol) into the region of lumbar enlargement dose-dependently reduced heat hyperalgesia, cold allodynia and mechanical allodynia for 2-6 h after injection, but had no effect on mechanical hyperalgesia. Li(+) had no significant effect on responses from control and sham-operated animals. Intrathecal injection of myo-inositol (2.5 mg) significantly reversed both the anti-hyperalgesic and anti-allodynic effect of Li(+). These findings suggest that intrathecal Li(+) suppresses neuropathic pain response in CCI rats through the intracellular phosphatidylinositol (PI) second messenger system in spinal cord neurons. Lithium (Li(+)) has already found widespread clinical application; these results suggest that its therapeutic utility may be extended to include treatment of neuropathic pain syndromes resulting from peripheral nerve injury.

PMID: 10692603 [PubMed - indexed for MEDLINE]

Anesthesiology 2000 Feb;92(2):493-9 Related Articles, Books, LinkOut



Intrathecally administered cGMP-dependent protein kinase Ialpha inhibitor significantly reduced the threshold for isoflurane anesthesia: implication for a novel role of cGMP-dependent protein kinase Ialpha.

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Department of Anesthesiology, University of Virginia Health Sciences Center, Charlottesville, USA.

BACKGROUND: Inhalational anesthetics have been shown to inhibit the nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) pathway. Previous studies indicated that inhibition of the NO-cGMP pathway decreased the level of consciousness and augmented anesthesia, analgesia, or sedation. The current study investigated the possible involvement of cGMP-dependent protein kinases (PKGs) as major effectors for the NO-cGMP pathway in the anesthetic state. METHODS: After initial baseline determination of the minimum alveolar concentration (MAC), a selective cGMP-dependent protein kinase Ialpha inhibitor, Rp-8-p-CPT-cGMPS, or an NO donor, (NOC-12), were injected intrathecally. Ten minutes later, MAC measurement was repeated. The rats also were evaluated for the presence of locomotor dysfunction by intrathecal administration of Rp-8-p-CPT-cGMPS and NOC-12 in conscious rats. RESULTS: Rp-8-p-CPT-cGMPS at 25, 50, 100, and 200 microg/10 microl produced a significant decrease from isoflurane control MAC of -43.1%, 164.5%, 305.0%, and 212.2%, respectively, which was not accompanied by significant changes in either blood pressure or heart rate. In contrast, NOC-12 at 100 microg/10 microl caused an increase from isoflurane control MAC of 235.8%, which was accompanied by significant decrease in blood pressure but not in heart rate. Rp-8-p-CPT-cGMPS (100 microg/10 microl) produced a significant reversal of isoflurane MAC increase induced by NOC-12 (100 microg/10 microl), which was accompanied by significant reversal of the reduction of blood pressure induced by NOC-12. Locomotor

activity was not changed. CONCLUSIONS: The results indicate that cGMP-dependent protein kinase Ialpha inhibitor not only markedly reduces MAC for isoflurane, but also completely blocks the NO-induced increase in isoflurane MAC, which suggests that cGMP-dependent protein kinase Ialpha may mediate the action for the NO-cGMP pathway in anesthetic mechanisms at the spinal cord level.

PMID: 10691237 [PubMed - indexed for MEDLINE]

Pain 2000 Feb;84(2-3):175-9 Related Articles, Books, LinkOut

Antihyperalgesic effects of intrathecally administered magnesium sulfate in rats.

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Intrathecal administration of MgSO(4) is reported to cause paralysis. However, the characteristic sensory disturbances have not been thoroughly investigated. We examined the effect of intrathecally administered MgSO(4) on the nociceptive threshold, using three different nociceptive measures, formalin test, hot plate test and paw pressure test in rats. The dose of MgSO(4) was 30, 100 or 300 microg. In acute nociceptive tests, intrathecal MgSO(4) did not cause any significant changes in the pain threshold. However, phase 2 of the formalin test was suppressed dose-dependently. It is known that spinal NMDA receptors are involved in the changes seen during the second (tonic) phase of the formalin test and in vitro studies showed that Mg(2+) can cause voltage-dependent blockade of NMDA receptor channel in the neurons of spinal dorsal horn. Thus, the suppressive effect of intrathecally administered MgSO(4) on the tonic inflammation-evoked behavior is mediated by the spinal NMDA receptors. Our results suggest that intrathecal administration of MgSO(4) may be therapeutically beneficial for patients with tonic pain involving the spinal NMDA receptors.

PMID: 10666522 [PubMed - indexed for MEDLINE]

Eur J Pharmacol 2000 Dec 1;409(1):37-43 Related Articles, Books, LinkOut

Effect of intrathecal administration of serotonin in chronic pain models in rats.

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The present study examined the effects of intrathecal (i.t.) administration of 5-hydroxytryptamine (5-HT; 0.1-100 microg) on mechanical hyperalgesia associated with neuropathic pain (chronic constriction of the sciatic nerve model and diabetic model) and inflammatory pain (carrageenan and polyarthritic models) in rats. Results demonstrated that the hyperalgesia observed in the mononeuropathic and diabetic rats was attenuated by 5-HT; the active dose, however, was 100- to 1000-fold higher than that required in normal rats, and was moderately effective. In the two experimental models of inflammatory pain, 5-HT was not markedly or similarly active. In the carrageenan model, 5-HT at the highest dose was only weakly effective whereas in the polyarthritic model it was inactive. Together, these results show that 5-HT has antinociceptive effects in several rat pain models, except in the model of diffuse pain (polyarthritic rats). Its antinociceptive effects in these models, however, are slight and differ from those observed in normal rats.

PMID: 11099698 [PubMed - indexed for MEDLINE]

Neuroreport 1999 Nov 26;10(17):3681-4 Related Articles, Books

Effects of intrathecal nocistatin on the flexor reflex and its interaction with orphanin FQ nociceptin.

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We studied the effects of intrathecal (i.t.) nocistatin, a peptide identified from the precursor of orphanin FQ/nociceptin (OFQ) on the spinal nociceptive flexor reflex in decerebrate, spinalized, unanesthetized rats and its interaction with i.t. OFQ. Nocistatin induced a moderate, non-dose-dependent facilitation of the flexor reflex without producing reflex depression whereas i.t. OFQ induced a biphasic dose-dependent facilitatory and inhibitory effect. The facilitatory effect of low dose (0.55 pmol) OFQ was significantly increased by nocistatin. On the other hand, the duration, but not magnitude, of reflex depression induced by a high (550 pmol) dose of OFQ was significantly shortened by 5.5 nmol nocistatin. Thus, nocistatin interacts with OFQ in a complex fashion, increasing excitation and reducing inhibition. No evidence was obtained for an antinociceptive effect of nocistatin in rat spinal cord.

PMID: 10619666 [PubMed - indexed for MEDLINE]

Ter Arkh 1999;71(10):38-40 Related Articles, Books

[Prevention of neuroleukemia by intrathecal administration of cytosar and methotrexate in acute lymphoblastic leukemia in adults].

[Article in Russian]

Filatov LB, Konstantinova TS, Shalaev VA.

AIM: To find out whether efficacy of neuroleukemia (NL) prevention by intrathecal administration of cytosar and methotrexate in remission induction phase in adult patients with acute lymphoblastic leukemia (ALL) depends on the risk factors. MATERIALS AND METHODS: The study covered 68 ALL patients. The diagnosis was made by cytological, histological and cytochemical tests of the peripheral blood and bone marrow. Immunophenotyping was performed in 48 patients. The treatment followed the German protocol 04.89 in modification of the Hematological Research Center of the Russian Academy of Medical Sciences. Prevention of NL consisted in intrathecal administration of cytosar (30 mg), methotrexate (15 mg) and dexamethasone (4 mg) once a week for 6 weeks beginning on induction day 1, further in consolidation, reinduction and once in 3 months in maintenance. Radiation of the brain was not conducted. Treatment of leuroleukemia consisted of intrathecal administration of the above drugs twice a week up to normalization of the liquor with subsequent their administration 5 times and craniospinal radiation in a dose 36 Gy. Further intrathecal administrations were made according to the protocol. RESULTS: Correlation was not found between age of the patients and frequency of neuroleukemia onset, between neuroleukemia incidence and peripheral blood leukocytosis at diagnosis. Results of NL prevention with cytosar and methotrexate given intrathecally in induction of remission (14.6% of neurorecurrences) are comparable with the results of NL prevention by radiation of the brain with intrathecal administration of methotrexate obtained in the German cooperative trial. CONCLUSION: NL prevention in ALL adult patients by intrathecal cytosar and methotrexate in remission induction is effective.

Publication Types:

- Clinical trial
- Multicenter study

PMID: 10612172 [PubMed - indexed for MEDLINE]

Eur Radiol 1999;9(9):1901-8 Related Articles, Books, LinkOut

A double-blind, prospective, randomized, multicenter group comparison study of iopromide 240 vs iohexol 240 in myelography.

Albrecht A, Golebiowski M, Kornienko VN, Nikitin V, Palmers Y, Trzebicki J, Twarkowski P, Wegener R.

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The aim of this study was to evaluate the safety and efficacy of iopromide 240 mgI/ml in comparison with iohexol 240 mgI/ml in myelography. A total of 421 patients in seven centers and four countries received an average of 11.9 ml of either iopromide 240 (278 patients) or iohexol 240 (143 patients) for X-ray and/or CT myelography in a randomized (2:1), prospective, double-blind study. All patients were followed up 3-4 h after the procedure, and 327 patients remained hospitalized for 24 h. In 82 patients an EEG was recorded prior to as well as 3-4 h and 24 h after myelography. Physical examinations, including measurement of vital signs, were performed in all patients at these time points. The results were subject to statistical analysis with the primary variable being the incidence of adverse events. Both contrast media (CM) were equally effective in terms of opacification. The rating for opacity was "good" or "excellent" in 88 % for both CM. Four patients (iopromide group: n = 3; iohexol group: n = 1) had transient EEG changes but did not show clinical symptomatology. The overall rate of patients experiencing any adverse event (AE) was 16.9 % for iopromide 240 and 14.0 % for iohexol 240. Equivalence testing was inconclusive; however, the results indicated equivalence. The rate for AEs considered as study-drug related was slightly lower with iopromide 240 than with iohexol 240 (7.2 vs 7.7 %, respectively). Neither unknown nor unexpected AEs known for myelographic X-ray CM nor serious adverse events were observed. Iopromide 240 and iohexol 240 are equally safe and effective and can be recommended for myelography.

Publication Types:

- Clinical trial
- Multicenter study
- Randomized controlled trial

PMID: 10602973 [PubMed - indexed for MEDLINE]

Clin Cancer Res 1999 Nov;5(11):3349-51 Related Articles, Books, LinkOut

Comment on:

- Clin Cancer Res. 1999 Nov;5(11):3394-402

Intrathecal depot cytarabine therapy: a welcome addition to a limited armamentarium.

Bleyer WA.

Publication Types:

- Comment
- Editorial

PMID: 10589743 [PubMed - indexed for MEDLINE]

Obes Res 1999 Nov;7(6):577-85 Related Articles, Books

Biologic response to peripheral and central administration of recombinant human leptin in dogs.

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OBJECTIVE: Because leptin is believed to act within the central nervous system, the objective of this study was to test that presumption by comparing the biologic responses to recombinant human leptin (rHuLeptin) when delivered either subcutaneously or intrathecally in a large animal species, the beagle dog. METHODS AND PROCEDURES: Adult beagle dogs were used for all studies (n=3 to 14). Treatment with rHuLeptin was either as daily subcutaneous or intermittent intrathecal injections. RESULTS: Subcutaneously administered rHuLeptin was absorbed with peak concentrations appearing at 2 to 4 hours. After intrathecal administration, cerebral spinal fluid concentrations declined in a bi-phasic manner with a terminal half-life of -6 to 8 hours. When lean beagles were given leptin subcutaneously, at 0.05 to 5 g/kg/day for up to 6 months, reductions in body weight (up to 30%) and food intake (up to 75%) were observed. Body fat loss was observed in both lean and obese dogs, and confirmed by dual energy X-ray absorptiometry and histology of adipose tissue. When rHuleptin was delivered intrathecally at 4 to 1000 microg/dose for up to 3 months, the primary effects observed were reductions in body weight and food intake. In general all findings reported in the intrathecal studies were consistent with those noted in the subcutaneous studies; however, the required intrathecal dose was substantially lower than that for subcutaneous delivery. DISCUSSION: These studies demonstrate that both subcutaneous and intrathecal treatment of rHuLeptin was associated with effects on body weight, food intake, and body fat in dogs. These results support the concept that the central nervous system is the probable primary site of action for leptin and suggest that rHuLeptin has similar physiologic activities that influence body weight, body fat, and metabolism in large animals to those reported previously in rodents.

PMID: 10574517 [PubMed - indexed for MEDLINE]

Br J Pharmacol 1999 Nov;128(5):941-4

Nociceptin (1 - 7) antagonizes nociceptin-induced hyperalgesia in mice.

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Nociceptin and its N-terminal fragment, nociceptin (1 7), were administered intrathecally (i.t.) into conscious mice. Nociceptin (3.0 fmol) produced a significant reduction in the nociceptive thermal threshold (hyperalgesia) measured as the tail-flick and paw-withdrawal responses. Nociceptin (1-7), injected i.t., at 150-1200 fmol had no significant effect. However, when nociceptin (1-7) (150 1200 fmol) was injected simultaneously with nociceptin (3.0 fmol), nociceptin-induced hyperalgesia was significantly reduced. Analgesia induced by a high dose (1200 pmol) of nociceptin was not antagonized by co-administration of nociceptin (1-7) (1200 fmol). These results suggest that N-terminal fragments of nociceptin formed endogenously could modulate the hyperalgesic action of nociceptin in the spinal cord.

PMID: 10556929 [PubMed - indexed for MEDLINE]

Anesthesiology 1999 Nov;91(5):1293-8

Intrathecal neostigmine and sufentanil for early labor analgesia.

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BACKGROUND: Recent efforts to improve the combined spinal epidural (CSE) technique have focused on adding opioids to other classes of analgesics. In this study, the authors used intrathecal neostigmine in combination with intrathecal sufentanil to investigate the usefulness of neostigmine for reducing side effects and prolonging the duration of sufentanil. METHODS: One hundred six healthy pregnant women in labor were enrolled in this study, which was divided into four phases. In all phases, patients received a CSE anesthetic while in the lateral position. In phase I, three groups of six women each received intrathecal neostigmine, 5, 10, or 20 microg, in an open-label, dose-escalating safety assessment. In phase II, 24 women received intrathecal sufentanil alone to establish an ED50 (dose that produces > 60 min of labor analgesia in 50% of patients). In phase III, an ED50 was established for

sufentanil combined with a fixed dose of neostigmine (10 microg). In phase IV, 40 women received either twice the ED50 of sufentanil alone or twice the ED50 of sufentanil plus neostigmine, 10 microg. RESULTS: Neostigmine alone had no adverse effects on maternal vital signs, fetal heart rate, or Apgar scores. Neostigmine, 20 microg, produced analgesia in one patient and severe nausea and vomiting in another. The ED50 for intrathecal sufentanil alone was 4.1 0.31 microg, and the ED50 for intrathecal sufentanil combined with neostigmine, 10 microg, was 3.0 0.28 microg. The duration of analgesia and side effects from double these ED50s (sufentanil, 9 microg, or sufentanil, 6 microg, plus neostigmine, 10 microg) were similar between groups. CONCLUSIONS: The 10-microg intrathecal neostigmine dose alone produced no analgesia or side effects, but reduced the ED50 of intrathecal sufentanil by approximately 25%. Additionally, doses approximately double these ED50s each produced a similar duration of analgesia and side effects, indicating intrathecal neostigmine shifts the dose-response curve for intrathecal sufentanil to the left.

Publication Types:

- Clinical trial
- Controlled clinical trial

PMID: 10551579 [PubMed - indexed for MEDLINE]

Anesthesiology 1999 Nov;91(5):1260-6 Related Articles, Books, LinkOut

Intrathecal bupivacaine in humans: influence of volume and baricity of solutions.

Malinovsky JM, Renaud G, Le Corre P, Charles F, Lepage JY, Malinge M, Cozian A, Bouchot O, Pinaud M.

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BACKGROUND: The effects of volume and baricity of spinal bupivacaine on block onset, height, duration, and hemodynamics were studied. METHODS: Ninety patients undergoing endoscopic urologic procedures were randomized to receive 10 mg of intrathecal bupivacaine at L2-L3 level in sitting position. In the operating room, commercial products were diluted as needed with NaCl 0.9% to obtain isobaric solutions (density, 1.005-1.008) or with NaC 10.9% and glucose 30% to obtain hyperbaric solutions (density, 1.031-1.037) of 2, 5, or 10 ml (six groups of 15 patients each). Three minutes after spinal injection the patients were placed in lithotomy position. Sensory blockade was assessed using pinprick and cold sensation tests, and motor blockade was assessed using a four-point scale. RESULTS: Onset times to maximal cephalad spread of spinal blockade were similar with isobaric and hyperbaric solutions. A greater maximal cephalad spread of anesthesia was obtained with diluted isobaric bupivacaine but was not associated with more hypotension. Volume

had no effect on cephalad extent of anesthesia with hyperbaric bupivacaine. Times for regression of anesthesia to L2 and offset of motor block were longer with isobaric than with hyperbaric solutions of bupivacaine. The intensity of motor blockade was decreased with diluted hyperbaric bupivacaine. No patient reported back pain. CONCLUSION: In this study, volume had no significant influence on either cephalad spread or duration of sensory blockade for either isobaric or hyperbaric bupivacaine. Time for offset of anesthesia was shorter with hyperbaric bupivacaine compared with isobaric solutions.

Publication Types:

- Clinical trial
- Randomized controlled trial

PMID: 10551575 [PubMed - indexed for MEDLINE]

Anesthesiology 1999 Nov;91(5):1239-45

Intrathecal ropivacaine for ambulatory surgery.

Gautier PE, De Kock M, Van Steenberge A, Poth N, Lahaye-Goffart B, Fanard L, Hody JL.

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BACKGROUND: The rationale of this study was to evaluate intrathecal ropivacaine for ambulatory surgery. METHODS: One hundred fifty patients with American Society of Anesthesiologists physical status 1 scheduled for knee arthroscopy were studied. Patients were randomly assigned to receive 4 ml of one of five isobaric intrathecal solutions: Patients in group 1 (n = 30) received 8 mg of bupivacaine; patients in group 2 (n = 30) received 8 mg ropivacaine; patients in group 3 (n = 30) received 10 mg ropivacaine; patients in group 4 (n = 30) received 12 mg ropivacaine; and patients in group 5 (n = 30) received 14 mg ropivacaine. The level and duration of sensory anesthesia were recorded along with the intensity and duration of motor block. Patients were interviewed to identify transient neurologic symptoms. RESULTS: Intrathecal ropivacaine 10 mg produced shorter sensory anesthesia and motor blockade than bupivacaine 8mg (152 44 min and 135 41 min vs. 181 44 min and 169 52 min, mean SD; $P < 0.05$). However, the quality of intraoperative analgesia was significantly lower in the 10-mg ropivacaine group ($P < 0.05$). Ropivacaine 12 mg produced sensory and motor block almost comparable to bupivacaine 8 mg. Ropivacaine 14 mg produced sensory and motor block comparable to ropivacaine 12 mg but significantly increased the time to void. No sign of transient radicular irritation were noted. CONCLUSION: Intrathecal ropivacaine 12 mg is approximately equivalent to bupivacaine 8 mg. At this dose, ropivacaine offers no significant advantage compared with

bupivacaine.

Publication Types:

- Clinical trial
- Randomized controlled trial

PMID: 10551572 [PubMed - indexed for MEDLINE]

Int J Clin Pharmacol Ther 1999 Oct;37(10):519-23

Addition of intrathecal midazolam to bupivacaine produces better post-operative analgesia without prolonging recovery.

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OBJECTIVE: The administration of midazolam by centroneuraxis route has been shown to produce segmental antinociception. This midazolam analgesia was found to enhance the effects of local anesthetics given in combination epidurally without any adverse effects. The present study was designed to evaluate the post-operative analgesic effect of intrathecal midazolam-bupivacaine mixture in patients undergoing knee arthroscopy. METHODS: Thirty healthy patients scheduled for knee arthroscopy were divided into two groups to receive either midazolam-bupivacaine mixture (group M; n = 15) or bupivacaine alone (group B; n = 15) intrathecally. Level of sensory block, sedation score, assessment of pain using visual analogue score were recorded in both groups at regular time intervals. Time to block regression, recovery to ambulation and ability to void were recorded and noted before discharge. RESULTS: A significantly higher VAS score was seen in group B patients as compared to the score observed in group M patients before discharge ($p<0.05$). All patients received rescue analgesia in group B at a mean duration of 258 46.8 minutes whereas only one patient in group M required supplemental analgesia within this period. Time to regression of sensory analgesia to L5-S1 level was longer in group M (26767.38) as compared to group B (229.841.4) ($p<0.05$). Blood pressure, heart rate, oxygen saturation and sedation score showed no differences between the groups. Neither motor block nor time to void were prolonged with the addition of midazolam to bupivacaine. CONCLUSION: The results suggest that addition of midazolam to bupivacaine intrathecally provided better post-operative analgesia without any adverse effects.

Publication Types:

- Clinical trial
- Randomized controlled trial

PMID: 10543321 [PubMed - indexed for MEDLINE]

Brain Res 1999 Sep 4;840(1-2):92-8

Epidural resiniferatoxin induced prolonged regional analgesia to pain.

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Adequate treatment of cancer pain remains a significant clinical problem. To reduce side effects of treatment, intrathecal and epidural routes of administration have been used where appropriate to reduce the total dose of agent administered while achieving regional control. Resiniferatoxin (RTX), an ultrapotent capsaicin analog, gives long-term desensitization of nociception via C-fiber sensory neurons. We evaluate here the analgesic effect on rats of epidurally administered RTX, using latency of response to a thermal stimulus in unrestrained animals. Results were compared with those for systemically administered RTX. Vehicle or graded doses of RTX were injected subcutaneously (s.c.) or through an indwelling lumbar (L4) epidural catheter as a single dose. Both routes of application of RTX produced profound thermal analgesia, reaching a plateau within 4-6 h and showing no restoration of pain sensitivity over 7 days. Vehicle was without effect. For the epidural route, the effect was selective as expected for the targeted spinal cord region, whereas the subcutaneous administration of RTX had a generalized analgesic effect. At doses yielding a tripling of back paw withdrawal latency, epidural treatment was 25-fold more effective than the subcutaneous route of application. Consistent with the regional selectivity of the lumbar epidural route, the front paws showed no more effect than by systemic RTX treatment. Binding experiments with [3H]RTX provided further evidence of the segmental desensitization induced by epidural RTX. We conclude that epidural administration of RTX at the lumbar spinal level produces profound, long-lasting, segmental analgesia to C-fiber mediated pain in the rat.

PMID: 10517956 [PubMed - indexed for MEDLINE]

AJR Am J Roentgenol 1999 Oct;173(4):1109-15

Intrathecal gadolinium-enhanced MR myelography and cisternography: a pilot study in human patients.

Zeng Q, Xiong L, Jinkins JR, Fan Z, Liu Z.

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OBJECTIVE: This study was designed to evaluate the safety, MR imaging characteristics, and clinical response to intrathecal gadopentetate dimeglumine (gadolinium) administration in human patients. SUBJECTS AND METHODS: Eleven adult patients were included in this prospective study. Via lumbar puncture, a single dose of either 0.2 ml, 0.5 ml, or 1.0 ml of gadolinium (500 mmol/l) mixed with 5 ml of previously removed CSF was slowly injected into the lumbar subarachnoid space. Immediate and delayed MR imaging were subsequently carried out using a 1.0-T magnet. RESULTS: No patient manifested gross behavioral changes, neurologic alterations, or seizure activity. The intrathecal gadolinium-enhanced MR myelography revealed disk herniation (n = 4), posttraumatic spinal stenosis (n = 3), postsurgical noncommunicating cyst (n = 1), myelitis (n = 1), intradural extramedullary mass formation (n = 1), and intradural vascular malformation (n = 1). CONCLUSION: This pilot study shows the relative safety and feasibility of low-dose intrathecal gadolinium administration. The potential clinical applications include the evaluation of obstructions and communications of the subarachnoid space, spontaneous or traumatic CSF leaks, and CSF dynamics. Additional animal and human studies must be performed to further evaluate the long-term safety and to prove the clinical applications of this procedure in a larger number of subjects.

PMID: 10511188 [PubMed - indexed for MEDLINE]

Cancer 1999 Oct 1;86(7):1347-53

Survival of patients with high grade glioma treated with intrathecal thiotriethylenephosphoramide for ependymal or leptomeningeal gliomatosis.

Witham TF, Fukui MB, Meltzer CC, Burns R, Kondziolka D, Bozik ME.

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BACKGROUND: The diagnosis of leptomeningeal dissemination of malignant glioma (meningeal gliomatosis) is associated with poor survival. Intrathecal (IT) chemotherapeutic agents used to achieve tumor control and improve survival include methotrexate, cytosine arabinoside (ara-C), thiotriethylenephosphoramide (thio-TEPA), neocarzinostatin, and 3-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-1-(2-chloroethyl)-1-nitros ourea hydrochloride (ACNU). Little information exists about survival following administration of IT chemotherapy. The authors report survival data from a series of patients with supratentorial anaplastic astrocytoma (AA) or

glioblastoma multiforme (GBM) treated for ependymal or leptomeningeal gliomatosis with IT thio-TEPA. METHODS: The authors reviewed the records of 14 patients treated between 1991 and 1997 (GBM: n = 9; AA: n = 5). All patients were diagnosed with ependymal (n = 8) or leptomeningeal (n = 6) dissemination of tumor on the basis of clinical signs and symptoms, ependymal or leptomeningeal contrast enhancement on magnetic resonance imaging (MRI), and/or cerebrospinal fluid analysis. All 14 patients underwent placement of a ventricular reservoir system and subsequent instillation of IT thio-TEPA on a weekly basis for 6-12 weeks. Response to treatment was evaluated clinically and by MRI at intervals of 1-3 months and 3-6 months from the initiation of IT thio-TEPA. Data on survival from the time of diagnosis of dissemination was assessed. RESULTS: The median survival, from the time of diagnosis of ependymal or leptomeningeal dissemination, of patients who received IT thio-TEPA was 10 months (AA = 19 months; GBM = 10 months). Five of 14 patients had a radiographic response to treatment within 6 months. The median survival of patients with a radiographic response was 15.5 months, compared with 10 months for nonresponders. No significant neurotoxicity or myelopathy was observed. CONCLUSIONS: Early treatment with IT thio-TEPA may result in improved survival with minimal morbidity. Radiographic response may predict prolonged survival.

Publication Types:

- Clinical trial

PMID: 10506724 [PubMed - indexed for MEDLINE]

Life Sci 1999;65(10):1059-66 Related Articles, Books, LinkOut

Antinociception produced by systemic, spinal and supraspinal administration of amiloride in mice.

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This study investigates the antinociceptive and antihyperalgesic action caused by i.p., i.t. or i.c.v. injections of amiloride when assessed against formalin, capsaicin-induced licking, acetic acid-induced writhing and glutamate-induced hyperalgesia in mice. The systemic, spinal and supraspinal administration of amiloride causes dose-related antinociception when assessed against acetic acid-induced writhing, formalin and capsaicin-induced licking. In addition, amiloride administered by the same routes produced graded inhibition of glutamate-induced hyperalgesia in mice. Together, these results suggest, that amiloride or its derivatives may constitute a strategy for the development of new antinociceptive drugs.

PMID: 10499873 [PubMed - indexed for MEDLINE]

Can J Anaesth 1999 Sep;46(9):856-60

Comparison of 0.25 mg and 0.1 mg intrathecal morphine for analgesia after Cesarean section.

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PURPOSE: To test the hypothesis that 0.1 mg intrathecal morphine plus NSAIDs provides satisfactory analgesia post-Cesarean section with fewer side effects than 0.25 mg intrathecal morphine. METHODS: Sixty women, scheduled for elective Cesarean section under spinal anesthesia, were randomized to receive either 0.1 mg or 0.25 mg intrathecal morphine combined with hyperbaric bupivacaine 0.75% and 20 microg fentanyl. All patients received a 100 mg indomethacin suppository at the end of surgery and 500 mg naproxen p.o. b.i.d. was started the evening of surgery and continued until discharge. A blinded researcher recorded the pain, pruritus, and nausea scores, the time to first request for additional analgesics, a visual analogue scale (VAS) satisfaction score, and the use of additional opioids, antipruritics, and/or antiemetics. RESULTS: Of the 60 patients enrolled, two were not included in the data analysis because of protocol violations leaving 30 patients in the 0.1 mg group and 28 in the 0.25 mg group. There were no differences in the VAS pain scores or the number of women requesting an opioid other than codeine between the two groups. The VAS pruritus scores in the 0.1 mg group were lower throughout the 24 hr ($P < 0.001$). Fewer women in the 0.1 mg group (4/30 vs 12/28) requested nalbuphine to treat itching ($P = 0.018$). Nausea scores were lower in the 0.1 mg group ($P < 0.001$). CONCLUSION: The use of 0.1 mg intrathecal morphine plus NSAIDs provides analgesia of similar quality to 0.25 mg but with fewer undesirable side effects following Cesarean section.

Publication Types:

- Clinical trial

PMID: 10490154 [PubMed - indexed for MEDLINE]