

Epidural Injections of Indomethacin for Postlaminectomy Syndrome: A Preliminary Report

J. Antonio Aldrete, MD, MS

Department of Anesthesiology, University of South Florida, College of Medicine, Tampa, and Aldrete Pain Care Center, Chipley, Florida

Since there have been side effects reported with the administration of corticosteroids epidurally, their application has been limited. Because some nonsteroidal antiinflammatory drugs have central and spinal antinociceptive actions, we have compared the effects of indomethacin (INM) given by the epidural route to methylprednisolone (MTP). This was a prospective, comparative study in an ambulatory pain care center. Two hundred six patients with recurrent low back pain (Visual Analog Scale >7) and radiculopathy after they had had 2 or more lumbar laminectomies with the diagnosis of "postlaminectomy syndrome" were randomly assigned to 1 of 3 groups. Group I (64 patients) was given 2 epidural injections of lyophilized INM 1 mg. Group II (60 patients) received 2 injections of 2 mg of INM at the same intervals. Group III (82 patients) was treated by 2 epidural injections of MTP 80 mg. In every case, the medication was diluted in 3 mL of 0.5% bupivacaine. Reductions of pain were assessed by changes in

the Visual Analog Scale; physical activities, attitude, and medication intake were graded by the Pain Progress Score recorded before each treatment and 2 wk after the last. After each injection, all patients had pain relief to Visual Analog Scale <3. Increased analgesia ($P < 0.05$) was noted when a double dose of INM was used (Group II) or when 80 mg of MTP was given. The total average scores of the Pain Progress Score showed significant differences at the second injection in Groups II and III only. Physical activity, emotional attitudes, and medication intake were also improved but the changes were not statistically significant. In conclusion, in this group of patients, INM produced adequate analgesia in Groups I and II, with evidence suggesting that 2 mg of INM may produce a similar degree of pain relief as 80 mg of MTP after the second injection. Other nonsteroidal antiinflammatory drugs may be explored in the future for the same purpose.

(Anesth Analg 2003;96:463-8)

The administration of epidural steroids has been indicated for low back pain from conditions such as degenerative disk disease and radiculopathy (1-3); however, some authors (4-6) have limited their use to 3 or 4 injections every 6 mo because of possible side effects (3,7). This policy has promoted the search for alternative nonsteroidal antiinflammatory drugs (NSAIDs) that affect pain transmission by other than the usual cyclooxygenase (Cox-2) inhibition mechanism (8-10). Attempting to find a substitute, we have administered two different dosages of indomethacin (INM) into the epidural space (ES) of patients with signs and symptoms of radiculopathy after spinal operations and compared their efficacy to that obtained from usual dosages of methylprednisolone (MTP).

Methods

Observations were made in 206 patients with recurrent low back pain after having had one or two lumbar laminectomies and having been diagnosed by either a neurosurgeon or an orthopedic surgeon as having "postlaminectomy syndrome." Patients with spinal fusions were excluded; however, a criterion for acceptance was at least 6 mo postoperation, excluding patients with pseudomeningocele, arachnoiditis, and/or recurrent pain from free disk fragments, as confirmed by a magnetic resonance imaging (MRI) study, and the complaint of lower back and extremity pain >7 according to the Visual Analog Scale (0 to 10). After having obtained an informed consent in accordance with the Aldrete Pain Care Center or the Destin Pain Care Center IRB, patients were told of the possible risks of the procedure and that the study medication (INM) had been used as an oral antiinflammatory but had only been used in a limited number of patients for epidural injection before and that he/she would be assigned, at random, to one of three groups receiving INM in two different dosages or MTP.

No financial interest is retained by the author on holdings by the manufacturers of any nonsteroidal antiinflammatory drugs.

Accepted for publication October 25, 2002.

Address correspondence and reprint requests to J. Antonio Aldrete, MD, MS, 938 Summit Place, Birmingham, AL 35243. Address e-mail to taldrete@arachnoiditis.com.

DOI: 10.1213/01.ANE.0000046012.19347.1B

Previously, a comprehensive medical history and physical examination had been done. Then the latest postoperative MRI films were reviewed with each of the patients to confirm the presence of pathology for which this therapy was indicated and to verify the presence and accessibility of at least one lumbar ES above the operated intervertebral space. Midline punctures were made with an 18-gauge Tuohy needle using the loss of resistance technique, with air, to find the ES. Randomly, the patients were assigned to receive epidurally either 1 mg of lyophilized, preservative-free INM Na trihydrated powder (Fig. 1) in Group I (64 patients), 2 mg of INM in Group II (60 patients), or 80 mg of MTP in Group III (84 patients). In every instance, the medications were diluted into 3 mL of 0.5% bupivacaine (BP) and the injections were repeated 2 wk later.

Control levels of pain and assessment of physical activity, medication intake, and emotional status were noted before initiating treatment. Subsequently, all patients were evaluated by a blinded individual when they returned for the second injection and also for the final evaluation recording the degree of pain relief as well as the changes of physical activities, medication needs, and emotional status according to the Pain Progress Score (11). The results were statistically analyzed by using the χ^2 method.

Results

In all patients, within 20 min after each injection, the pain level decreased to <3 on the Visual Analog Scale. The average pain levels were significantly reduced ($P < 0.05$) 2 wk after each treatment, as shown in Table 1. There was also improvement in physical activities, emotional attitude, and intake of pain-related medications; these changes, however, were not statistically significant. The average total scores were significantly increased in the patients receiving MTP, 2 wk after the first and the second injections, whereas in the groups treated with INM, a statistically significant difference was noted only 2 wk after the second injection. There were no instances of apparent dural puncture or high sensory or motor block noted, nor were there any other untoward effects typical of NSAID therapy such as rash, epigastric discomfort, or bruising.

Discussion

Although the administration of corticosteroids into the ES is often used for the treatment of low back pain, with radiculopathy (1-5), there is still debate concerning other specific indications (6,12,13), the dosage (1,14), the frequency (2,4), and the duration (5,7,12,14) of these treatments. There are also concerns regarding some deleterious metabolic effects from repeated administration (15,16) which have in part resulted in an

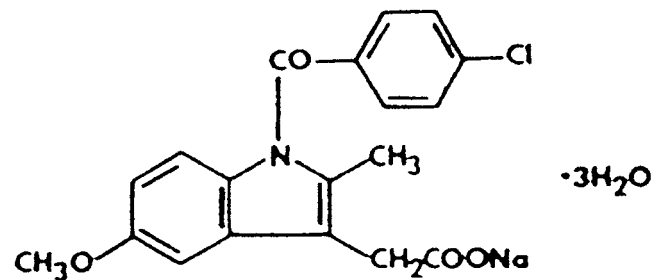


Figure 1. Indomethacin sodium trihydrate as lyophilized powder.

arbitrary consensus limiting them to 3 or 4 injections every 6 months. However, this apparent objection has limited the obvious therapeutic potential of corticosteroids because most of the alleged indications are chronic diseases that would not be fully treated in 3 or 6 months (1,14). Therefore, an alternative medication with antiinflammatory action is desirable. This is especially true in certain cases such as diabetic patients, who are in need of this therapeutic modality, but in whom the well known gluconeogenic effect of corticosteroids produces hyperglycemia. This alternative may also be indicated in patients allergic to corticosteroids, in cases of chronic heart failure, and in those who adamantly refuse to receive this type of medication for fear of gaining weight, or the possibility of bone fractures attributed to osteoporosis, etc. (Table 2).

Although NSAIDs were initially thought to act mostly peripherally because inflammation causes the induction of Cox-2 resulting in the liberation of prostanooids which sensitize peripheral nociceptor terminals fostering in localized hypersensitivity (17), their central effects have been suspected (9,10).

INM, one of the older NSAIDs, is supposed to produce analgesia by inhibition of prostaglandin (PGI) synthesis, which may also apparently account for its ability to suppress inflammation (18). In addition, its antipyretic action may also be attributed to inhibition of PGI synthesis in the central nervous system, resulting in vasodilation (8). It is the only NSAID commercially available in the United States in parenteral form, packaged in a lyophilized powder as 1-(4 chlorobenzyl)-5-methoxy-2-methyl-1H-indole-3 acetic acid with a pH of 6.5 (Fig. 1). Its labeled indication is for IM or IV administration for the occlusion of patent ductus arteriosus in newborns (19,20), presumably by the same mechanism, although this effect may be caused by a more complex process (21).

Dempsey et al. (22) showed that INM protected brain tissue when the middle cerebral artery was occluded in cats. Similarly, Guth et al. (23) and Simpson et al. (24), using two different spinal cord injury animal models, demonstrated that INM had a favorable effect on the recovery of locomotor function and cellular repair. These reports confirmed earlier observations by Hallenbeck et al. (25) who showed that a

Table 1. Average Changes on Pain Progress Score After Epidural Indomethacin (INM) 1 mg (Group I), INM 2 mg (Group II), and 80 mg of Methylprednislone (Group III)

Indices	Value of variables	Before 1st injection			Before 2nd injection			2 wk later		
		I	II	III	I	II	III	I	II	III
Pain intensity		0.52	0.61	0.54	1.27*	1.29*	1.36*	1.16*	1.21*	1.34*
Physical activity	1 = 4 to 7 level 2 = 0 to 3 level									
	0 = Activities severely limited by pain 1 = Activities slightly limited by pain 2 = Able to perform all expected duties	0.91	1.03	0.96	1.33	1.42	1.46	1.24	1.34	1.38
Emotional attitude	0 = Severely depressed, anxious, other 1 = Mild depression, insomnia	1.02	0.94	0.89	1.39	1.48	1.51	1.20	1.47	1.51
	2 = Adapts well and copes with pain									
Analgesic intake	0 = Parenteral opioid 1 = Oral opioid analgesic	1.43	1.23	1.18	1.46	1.51	1.62	1.36	1.44	1.52
	2 = NSAID or nonopioid analgesic									
Other pain-related medications	0 = Tranquilizers, hypnotics, muscle relaxants, antidepressants, others 1 = Muscle relaxants, antidepressants	1.12	0.96	0.89	1.22	1.24	1.34	1.31	1.42	1.51
	2 = Muscle relaxants only									
Total score		4.70	4.77	4.46	6.67	6.84	7.19*	6.77	8.18*	8.26*

NSAID = nonsteroidal antiinflammatory drug.
* *P* < 0.05 compared with levels before first treatment.

Table 2. Indications of Epidural Indomethacin

- a) After evidence of side effects of steroid administration
- b) Patients with diabetes mellitus
- c) Patients allergic to steroids
- d) Patients allergic to depo-type of medication
- e) Patients refusing to receive steroids
- f) Patients with chronic congestive heart failure

combination of PGI₂, INM, and heparin improved neurological recovery after spinal trauma in cats, and by Siegal et al. (26,27) who evaluated drugs that may protect from neural damage in an experimental neoplastic cord compression, finding that the combination of INM and dexamethasone afforded far more protection than either of the two drugs used separately. Also, in the neuraxis, INM is supposed to attenuate the nociceptive activity produced by chemical irritants (28). These observations are relevant because they seem to demonstrate a definitive protective effect of INM on neural tissue.

Clues that NSAIDs may produce pain modulation by central mechanisms were suggested by Ferreira et al. (29) and Ferreira (30) noting that the administration of NSAIDs into the cerebral ventricles inhibited the hyperalgesia evoked by carrageenan injected into rats' paws. Among other studies, Shyu et al. (31) showed that dental analgesia was produced in monkeys with intraventricular aspirin, and Groppetti et al. (32) demonstrated that aspirin also reduced the firing of thalamic neurons evoked by noxious stimulation in rats. Jurna and Brune (33) confirmed the supraspinal mechanisms of NSAIDs on antinociceptive effects as they

noted that diclofenac, ibuprofen, and INM reduced single-neuron activity in the rat's thalamus after sural nerve C fiber stimulation.

Since the earlier report by Yaksh (34) demonstrating that intrathecal aspirin had a dose-dependent depression on rats' writhing behavior produced by intraperitoneal injection of acetic acid, others have shown that NSAIDs have analgesic effects on spinal nociceptive processing (35,36), such as dose-dependent suppression of delayed hyperalgesia (37). This was also confirmed by a reversed effect on thermal hyperalgesia as tested in different animal models by Malmberg and Yaksh (38). More specifically, when given intrathecally, INM (in large doses) inhibited the electrophysiological responses of dorsal horn nociceptive neurons evoked by formalin injection (39). The release of prostanooids in inflammation has also been linked to sensitization of peripheral terminals (40) and likely is responsible for the hypersensitivity in noninjured, neighboring adjacent tissue, because of increased neuronal excitability in the spinal cord (17,41).

Yaksh (42) also noted that some NSAIDs injected intrathecally may reduce paw scratching in rats, even when dosages were considerably smaller than those necessary to produce the same effect when given systemically. Furthermore, a quantitative study attempting to establish an ascending potency of NSAIDs by the usual formalin test in rats placed INM at the top of this group of drugs (43). These effects have been attributed to mechanisms dependent on NMDA receptors and PGI inhibition at the posterior spinal horn where Cox-2 has a relevant role (29,44). However, the

precise mechanisms of these effects are likely more complex than we now understand (45,46), as confirmed by Masue et al. (47) who demonstrated that neither systemic nor epidural ibuprofen suppressed nitroglycerin-induced hyperalgesia in rats, whereas epidural INM (10–100 μg) or diclofenac (10–1000 μg) suppressed it. These observations have been supported by Dirig et al. (48) and Samad et al. (49) who demonstrated that prostanoid production in the spinal cord after Cox-2 induction in dorsal horn neurons likely contributes to the establishment and maintenance of inflammatory hypersensitivity.

In addition to the usual application in chronic arthritis and other inflammatory processes (17,18), other NSAIDs in general, and specifically INM, had been given to patients IV to reduce perioperative pain (50,51) and as an adjunct to conventional analgesics (50,52–54). Enticed by the fact that basic research has shown that these drugs possibly have central (34,35,37) and spinal actions (36,39,40), it was expected that clinical studies using NSAIDs epidurally would follow.

In our early clinical observations with INM administered in the ES subsequent to steroid treatments, adequate pain relief was achieved without evidence of neurological deficit (55). The apparent initial improvement was similar whether patients received 1 or 2 mg of INM according to whether they had 1 or 2 laminectomies, but it was significantly increased ($P < 0.5$) at the second and third week postinjection, only when 2 mg was given. However, no comparison was made to the most commonly used steroid, MTP, as it was done in the current comparative, randomized clinical study that included three different groups of patients, having similar diagnosis after one laminectomy. Those results suggested that, concerning the duration of posttreatment pain relief, 2 mg of INM was equivalent to 80 mg of MTP. No permanent adverse effects were noted that could be attributed to INM; the minimal evanescent numbness noted in approximately 7% of those patients was believed to be attributed to the concomitant injection of 4 mL of 0.5% BP. Therefore, only 3 mL was administered in the current study. No such temporary sensory deficit was observed in our study. The “postlaminectomy syndrome” was chosen as a model for these studies because it is usually manifested by a relatively consistent lumbar localization of the pain, usually with unilateral radiculopathy caused by epidural fibrosis that can be confirmed with MRI, without having the complicating factors derived from a fusion (56,57).

In addition to all prior animal studies in which various NSAIDs were injected into the neuraxis without noticing an obvious neurological deficit, Guevara et al. (58) infused intrathecally 2 groups of adult rats with either INM in saline 20 $\mu\text{g}/\text{day}$ in 10 animals, or 0.9% saline only in another similar group. After

11 days of continuous infusion, the animals were killed and a neuropathologist examined the spinal cords (blindly). Cellular infiltration typical of chronic inflammation was seen in two rats of each group, which was attributed to the presence of the catheter; only one rat in the group that received INM had pial venous congestion. No neurological deficit or behavioral abnormality was seen in any of the rats.

In patients also, Devoghel (59) relieved intractable pain with small doses of lysine-acetylsalicylate administered intrathecally. Lauretti et al. (60) produced analgesia in patients having cancer pain with epidural infusions of two different NSAIDs. On this premise, based on our earlier observations (55) and on the results from this study in patients, it may be stated that INM seems to be safe and effective in temporarily relieving radicular pain experienced by patients after spinal operations, with similar results as those noted after MTP. What the outcome may be after larger doses or more INM injections are given, is not yet known. However, it is likely that the administration of NSAIDs by the peridural and intrathecal routes will expand. As more is learned about their peripheral and central mechanisms to produce analgesia, further indications for NSAIDs may be found and they may, at least in part, replace opioids for this purpose. Although newer and safer drugs are currently being developed, it does not mean that medications already in use such as salicylic acid, ketorolac, ketoprofen, and in our particular case, INM may be further studied as an injectate or as an infusate in the neuraxis while the search for current optimal therapeutic dosages is conducted (61). For now, an effective injectable NSAID such as INM may be used, alternating with a series of steroid epidural injections, to minimize the side effects of corticosteroids. Other possible indications of epidural INM are shown in Table 2; contraindications may include allergy to INM and bleeding disorder.

The large proportion of patients in this study who responded to epidural injections of MTP or INM, combined with BP, is at variance with other studies of the outcome of epidural injection of corticosteroids (62–64). The reasons for this discrepancy may include the shorter follow-up time of two weeks in the present study, the treatment only of postlaminectomy syndrome in the present study, after multiple laminectomies, compared with more heterogeneous populations in prior studies. Further studies with follow-up at later times after MTP administered by epidural injection are required.

Frédérique H. Montpetit, NP, and Sonya C. Johnson, LPN, assisted in the evaluation of these patients and the preparation of the manuscript.

References

1. Raj PP. Epidural steroid injections. *Pain Digest* 1999;9:235-40.
2. Bogduk N. Current guidelines in the use of epidural steroids: reports from Australia, Belgium, Norway, the United Kingdom, and the USA. *Pain Digest* 1999;9:226-34.
3. Hickey RF. Outpatient epidural steroid injections for low back pain and lumbosacral radiculopathy. *N Z Med J* 1987;100:594-6.
4. Winnie AP, Hartman JT, Meyer HL, et al. Pain clinic: extradural and intradural corticosteroids for sciatica. *Anesth Analg* 1972;51:990-9.
5. Abram SE. Perceived dangers from intraspinal steroid injections. *Arch Neurol* 1989;46:719-20.
6. Ridley MG, Kingsley GH, Gibson T, Graham R. Outpatient lumbar epidural corticosteroid injection in the management of sciatica. *Br J Rheumatol* 1988;27:295-9.
7. Saal JA, Saal JS, Herzog RJ. The national history of lumbar disc extrusion treated non-operatively. *Spine* 1990;15:683-6.
8. Brune K. Spinal effect of antipyretic analgesics. *Drugs* 1994;47(Suppl 5):21-7.
9. Meller ST, Gebhart GF. Spinal mediators of hyperalgesia. *Drugs* 1994;47(Suppl 5):10-20.
10. Cashman J, McAnulty G. Nonsteroidal anti-inflammatory drugs in perisurgical pain management: mechanism of action and rationale for optimum use. *Drugs* 1995;49:51-70.
11. Aldrete JA. The pain progress score: a tool to measure therapeutic progress. *Reg Anesth* 1995;20:55.
12. Weisz GM. Epidural use of methylprednisolone acetate (Depo-Medrol). *Med J Aust* 1991;154:854.
13. Fukusaki M, Kobayashi I, Hara T, et al. Symptoms of spinal stenosis do not improve after epidural steroid injections. *Clin J Pain* 1998;14:148-51.
14. Benzon HT. Epidural steroid injections for low back pain and lumbosacral radiculopathy. *Pain* 1986;24:277-85.
15. Jacobs S, Pullan PT, Potter JM, et al. Adrenal suppression following extradural steroids. *Anaesthesia* 1983;38:953-6.
16. Kay J, Finding NW, Ratt H. Epidural triamcinolone suppresses the pituitary-adrenal axis in human subjects. *Anesth Analg* 1994;79:501-5.
17. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain of pain. *Science* 2000;288:1765-8.
18. Jeremy N, Cashman JN. The mechanism of action of NSAIDs in analgesia. *Drugs* 1996;52:15-23.
19. Berry FA. Neonatal anesthesia. In: Barash PG, Cullen BF, Stoelting RK, eds. *Clinical anesthesia*. Philadelphia: JB Lippincott, 1989:1275-6.
20. Indocin (indomethacin sodium trihydrate) by Merck & Co. In: *Physician's desk reference*. Montvale, NJ: Medical Economics, 1997:1684-5.
21. Blackham A, Norris AA, Woods FA. Models for evaluation of the anti-inflammatory effects of inhibitors of arachidonic acid metabolism. *J Pharm Pharmacol* 1985;37:787-93.
22. Dempsey RJ, Roy NW, Meyer KL, et al. Indomethacin-mediated improvement following middle cerebral artery occlusion in cats. *J Neurosurg* 1985;62:874-81.
23. Guth L, Zhang Z, DiProspero NA, et al. Spinal cord injury in the rat: treatment with bacterial lipopolysaccharide and indomethacin enhances cellular repair and locomotor function. *Exp Neurol* 1994;126:76-87.
24. Simpson RK, Baskin DS, Dudley AW, et al. The influence of long-term nifedipine or indomethacin therapy on neurologic recovery from experimental spinal cord injury. *J Spinal Disord* 1991;4:420-7.
25. Hallenbeck JM, Jacobs TP, Faden AI. Combined PGI₂, indomethacin and heparin improves neurological recovery after spinal trauma in cats. *J Neurosurg* 1983;58:749-54.
26. Siegal T, Siegal T, Shapira Y, et al. Indomethacin and dexamethasone treatment in experimental neoplastic spinal cord compression. I. Effect on water content and specific gravity. *Neurosurgery* 1988;22:328-33.
27. Siegal T, Shohami E, Shapira Y, et al. Indomethacin and dexamethasone treatment in experimental neoplastic spinal cord compression. II. Effect on edema and prostaglandin synthesis. *Neurosurgery* 1988;22:334-9.
28. Vane JR, Botting RM. Mechanisms of action of anti-inflammatory drugs. *Scand J Rheumatol* 1996;25:9-21.
29. Ferreira SH, Lorenzetti BB, Correa FMA. Central and peripheral anti-analgesic action of aspirin-like drugs. *Eur J Pharmacol* 1978;53:39-48.
30. Ferreira SH. Prostaglandins: peripheral and central analgesia. In: Bonica JJ, Albé-Fessard DG., eds. *Advances in pain research and therapy*. Philadelphia: Raven Press, 1983;5:627-34.
31. Shyu KW, Lin MT, Wu TC. Possible role of central serotonergic neurons in the development of dental pain and aspirin-induced analgesia in the monkey. *Exp Neurol* 1984;84:179-87.
32. Groppetti A, Braga PC, Biella G, et al. Effect of aspirin on serotonin and met-enkephalin in brain: correlation with the antinociceptive activity of the drug. *Neuropharmacology* 1988;27:499-505.
33. Jurna I, Brune K. Central effect of the nonsteroidal anti-inflammatory agents indomethacin, ibuprofen and diclofenac, determined in C fibre-evoked activity in single neurons of the rat thalamus. *Pain* 1990;41:71-80.
34. Yaksh T. Central and peripheral mechanisms for the analgesic action of acetyl salicylic acid. In: Barrett JHM, Mustard JF, eds. *Acetyl salicylic acid: new uses for old drugs*. New York: Raven Press, 1982:137-151.
35. Taiwo VO, Levine JD. Prostaglandins inhibit endogenous pain control mechanisms by blocking transmission at spinal noradrenergic synapses. *J Neurosci* 1988;8:1346-9.
36. Bjorkman R, Hedner J, Hedner T, Henning M. Central, naloxone-reversible antinociception by diclofenac in the rat. *Naunyn Schmiedebergs Arch Pharmacol* 1990;342:171-6.
37. Malmberg AB, Yaksh TL. Antinociceptive actions of spinal nonsteroidal anti-inflammatory agents on the formal test in the rat. *J Pharmacol Exp Ther* 1992;263:136-46.
38. Malmberg AB, Yaksh TL. Hyperalgesia mediated by spinal glutamate or substance P receptor blocked by spinal cyclooxygenase inhibition. *Science* 1992;257:1276-9.
39. Chapman V, Dickenson AH. The spinal and peripheral roles of bradykinin and prostaglandins in nociceptive processing in the rat. *Eur J Pharmacol* 1992;219:427-33.
40. McClesley EW, Gold MS. Ion channels of nociception. *Annu Rev Physiol* 1999;61:835-56.
41. Brune K. Spinal effects of antipyretic analgesics. *Drugs* 1994;47:21-7.
42. Yaksh TL. The spinal pharmacology of facilitation of afferent processing evoked by high threshold afferent input of the post-injury pain state. *Curr Opin Neurol Neurosurg* 1993;6:250-6.
43. Wang BC, Li D, Hillman DE, et al. The antinociceptive effect of S-(+)-ibuprofen in rabbits: epidural versus intravenous administration. *Anesth Analg* 1995;80:92-6.
44. McKomark K. Nonsteroidal anti-inflammatory drugs and spinal nociceptive processing. *Pain* 1994;59:9-43.
45. Cuss JJ, Lipsky PE, Postlethwaite AE, et al. Correlation of serological indicators of inflammation with effectiveness of nonsteroidal anti-inflammatory drug therapy in rheumatoid arthritis. *Arthritis Rheum* 1990;33:19-28.
46. Cherng CH, Wong CS, Ho ST. Spinal actions of nonsteroidal anti-inflammatory drugs. *Acta Anaesthesiol Sin* 1996;34:81-8.
47. Masue T, Dohi S, Asano T, et al. Spinal antinociceptive effect of epidural nonsteroidal anti-inflammatory drugs on nitric oxide-induced hyperalgesia in rats. *Anesthesiology* 1999;91:198-206.
48. Dirig D, Konin GP, Isakson PC, Yaksh TL. Effect of spinal cyclooxygenase inhibitors in rats using the formalin test and *in vitro* prostaglandin E₂ release. *Eur J Pharmacol* 1997;331:155-60.
49. Samad TA, Moore KA, Sapirstein A, et al. Interleukin-1B-mediated induction of Cox-2 in the CNS contributes to inflammatory pain hypersensitivity. *Nature* 2001;410:471-5.
50. Tigerstedt I, Tammisto T, Neuvonen PJ. The efficacy of intravenous indomethacin in prevention of postoperative pain. *Acta Anaesthesiol Scand* 1991;35:535-40.

51. Turner GA, Gorringer J. Indomethacin as adjunct analgesia following open cholecystectomy. *Anaesth Intensive Care* 1994;22:25-9.
52. Joris J. Efficacy of nonsteroidal anti-inflammatory drugs in postoperative pain. *Acta Anaesthesiol Belg* 1996;47:115-23.
53. Dahl JB, Kehlet H. Nonsteroidal anti-inflammatory drugs: rationale for use in severe postoperative pain. *Br J Anaesth* 1991;66:703-12.
54. Pavy T, Medley C, Murphy DF. Effect of indomethacin on pain relief after thoracotomy. *Br J Anaesth* 1990;65:624-7.
55. Aldrete JA, Sued JA, Aldrete VT, Williams SF. Epidural injections of indomethacin for postlaminectomy syndrome. *Reg Anesth Pain Med* 1999;24:70.
56. Burton CV. Causes of failure of surgery of the lumbar spine: ten year follow-up. *Mt Sinai J Med* 1991;58:183-9.
57. Carrol SE, Wiesel SW. Neurologic complications and lumbar laminectomy. *Clin Orthop* 1992;25:14-23.
58. Guevara U, Aldrete JA, DeLille R, et al. Evaluación de la neurotoxicidad de la indometacina administrada en forma crónica en el espacio intratecal a ratas. *Rev Esp Dolor* 2000;7:86-9.
59. Devoghel JC. Small intrathecal doses of lysine-acetylsalicylate relieve intractable pain in man. *J Int Med Res* 1983;11:90-1.
60. Lauretti GR, Reis MP, Mattos AL, et al. Epidural nonsteroidal anti-inflammatory drugs for cancer pain. *Anesth Analg* 1998;86:117-8.
61. Bannwarth B, Netter P, Pourel J, et al. Clinical pharmacokinetics of nonsteroidal anti-inflammatory drugs in the cerebrospinal fluid. *Biomed Pharmacother* 1989;43:121-6.
62. Watts RW, Silagy CA. A meta-analysis on the efficacy of epidural corticosteroids in the treatment of sciatica. *Anaesth Intensive Care* 1995;23:564-9.
63. Abram SE. Treatment of lumbosacral radiculopathy with epidural steroids. *Anesthesiology* 1999;91:1937-41.
64. Koes BW, Scholten RJ, Mens JM, Boulter LM. Efficacy of epidural steroid injections for low back pain and sciatica: a systematic review of randomized clinical trials. *Pain* 1995;63:279-88.

Attention Authors!

Submit Your Papers Online

You can now have your paper processed and reviewed faster by sending it to us through our new, web-based Rapid Review System.

Submitting your manuscript online will mean that the time and expense of sending papers through the mail can be eliminated. Moreover, because our reviewers will also be working online, the entire review process will be significantly faster.

You can submit manuscripts electronically via www.rapidreview.com. There are links to this site from the Anesthesia & Analgesia website (www.anesthesia-analgesia.org), and the IARS website (www.iars.org).

To find out more about Rapid Review, go to www.rapidreview.com and click on "About Rapid Review."