

Intrathecal opioids

YVES VEILLETTE, MD, FRCPC

Opioid receptors were identified in the central nervous system in 1971.¹ Later, in 1977, these receptors were precisely localized in the posterior horn of the spinal cord.² Other receptors, discovered in peripheral tissues (eg, intestines, inflammatory cells, cutaneous tissue) are now the subjects of intensive research.³⁻⁵ These advances, along with the discovery of endogenous opioids (endorphins, dynorphins, and enkephalins),⁶ were the result of animal studies that demonstrated the analgesic potency of intrathecally-administered opioids.⁷ In 1979, Wang used intrathecal morphine for the first time to alleviate pain in cancer patients.⁸ The histochemical safety of morphine was revealed in autopsies and led to its use in controlling acute, chronic, and cancer pain.

This article discusses the intrathecal use of opioids to manage pain. We will start with a brief examination of the physiology of opioid receptors, their mechanisms of action, and certain pharmacokinetic considerations. The discussion will then proceed to clinical applications in situations of acute pain (perioperative and obstetrical), as well as chronic and cancer pain. Finally, there is a review of the technical considerations (monitoring, side effects, and complications).

PHYSIOLOGY

Painful stimuli trigger neural transmission via A-delta and C-type somatosensory fibers. These fibers relay their information to the secondary sensory neurons found in large numbers in the substantia gelatinosa of the posterior horn of the spinal cord. This is where modulation from a descending system takes place and is mediated by different substances including endogenous endorphins. While various receptors in the nervous system have been identified (μ , κ , and δ), it is the κ and δ receptors that have a dominant action at the spinal level, while the μ receptors are mainly responsible for supraspinal action. Other receptors exist (ϵ and σ), but are not specific to opioids (Table 1).¹⁰

MECHANISM OF ACTION

Opioid receptors are located in the glycoprotein membranes and are coupled with G proteins that modulate the ionic conduction of calcium and potassium. When stimulated, the μ and δ receptors open a potassium channel, increasing conductance, whereas the κ receptors inhibit the entrance of calcium. In both cases, the ensuing hyperpolarization inhibits neuronal activity.¹¹ Opioid tolerance could be caused by a decrease in the coupling of μ receptors and protein G receptors.¹²

PHARMACOKINETICS

The effectiveness of intrathecal opioids depends on their bioavailability. Penetration into medullary tissue is influenced by their molecular weight, degree of ionization, and lipophilicity. Fentanyl and meperidine are absorbed more rapidly than morphine for these reasons. They bind more solidly to neural tissue. Little is known about opioid metabolism in the spinal cord, but it plays a secondary role in the cessation of analgesic activity since clearance is the primary factor responsible. Clearance depends on diffusion along the neuraxis, as well as vascular absorption. The drug reaches the cerebellomedullary cistern via diffusion where it is absorbed by the arachnoid granulations. This is particularly true in the case of morphine. The more lipophilic products are reabsorbed at the site through spinal vasculature.¹³

Committee for Continuing Medical Education
Department of Anesthesiology
University of Montreal

Pierre Drolet, MD
Chairman and Editor
Maisonneuve-Rosemont Hospital

Jean-François Hardy, MD
Chairman of the Department of Anesthesiology,
University of Montreal

François Donati, MD
Maisonneuve-Rosemont Hospital

Edith Villeneuve, MD
Ste-Justine Hospital

Robert Blain, MD
Montreal Heart Institute

Normand Gravel, MD
CHUM

Robert Thivierge, MD
Vice-Dean
Continuing Education
University of Montreal

University of Montreal
Department of Anesthesiology
Faculty of Medicine
C.P. 6128, Succursale Centre-Ville
Montréal (Québec) H3C 3J7
Pavillon principal, bureau S-712
Tel: (514) 343-6466
Fax: (514) 343-6961
E-mail: anesth@medclin.
umontreal.ca

Université 
de Montréal
Faculty of Medicine
Department of Anesthesiology

The editorial content of *Anesthesiology Rounds* is determined solely by the Department of Anesthesiology of the University of Montreal Faculty of Medicine

This issue and CME questionnaire
are available on the Internet
www.anesthesiologyrounds.ca

TABLE 1: Opioid receptors, sub-types and physiological effects

Receptor	Sub-Type	Effects
Mu	Mu ₁	Supraspinal analgesia
	Mu ₂	Physical dependence Euphoria Sedation Respiratory depression
Delta	Delta _{1,2}	Constipation Orthostatic hypotension
Kappa	Kappa _{1,2,3}	Arteriolar/venous dilatation Spinal analgesia Euphoria Potentiates analgesia of Mu receptors Spinal analgesia Sedation Pupillary constriction Supraspinal analgesia (K 3)

Adapted from Lipman AG, Jackson KC. Opioids. In Warfield C, Bajwa Z, eds. *Principles and Practice of Pain Management*, 2nd ed. New York: McGraw-Hill, 2001

CLINICAL APPLICATIONS

There are numerous clinical applications for the intrathecal opioids (Table 2); however, trauma-induced and non-surgical pain are not discussed in this article since there are few clinical studies on these subjects.

ACUTE PAIN

For acute pain, the usefulness of morphine administered via the spinal route is limited by the time factor. Indeed, anesthesiologists prefer using the epidural route when a catheter intended for prolonged administration must be placed. The introduction of a catheter into the subarachnoid space requires a bigger needle than the one used for simple spinal anesthesia and this may increase the incidence of headache. The neurological effects associated with the use of spinal microcatheters and local anesthetics¹⁴ have likely discouraged their use with opioids. Hence, intrathecal opioid administration is generally used as a complementary technique during the operative period, for short-term postoperative analgesia (until oral medications can be used), or in obstetrical practice, where opioids are administered alone or in combination during labour, delivery, and for caesarean sections.

Perioperative administration

Intrathecal opioids have been used in the perioperative period with various local anesthetics. Due to its potential neurotoxicity, lidocaine was replaced by bupivacaine (in low doses) for short surgical procedures.¹⁵ Adding opioids to low-dose bupivacaine can help reduce the number of unsuccessful spinal anesthetics.¹⁶ For example, in one study, the addition of 10 µg of fentanyl to 3 ml of bupivacaine 0.17% pro-

TABLE 2: Therapeutic applications of intrathecal opioids

Acute pain

- Perioperative pain
- Postoperative pain
- Perinatal pain
- Trauma-induced pain
- Non-surgical pain (angina, myocardial infarction, herpetic neuralgia, pyelonephritis, thrombophlebitis)

Non-cancerous chronic pain

- Ischemia, back pain, neuropathy, mixed pain.

Cancer pain

duced anesthesia sufficient for knee arthroscopy in all subjects. On the other hand, 6 of 25 patients in a control group where bupivacaine was used alone at the same dose complained of insufficient anesthesia. Several studies report similar findings with different surgical procedures. However, the doses studied varied and suggesting an ideal “local-opioid anesthesia” combination is difficult (Table 3).

A dose of 20 µg of fentanyl prolongs the sensory block associated with 50 mg of isobaric lidocaine, but it has no effect on the sensory block induced by 100 mg of procaine.¹⁷

Postoperative analgesia

The administration of spinal opioids also improves postoperative analgesia. Because of its long duration of action, morphine is the agent of choice for anesthesiologists. However, it is recommended that patients be hospitalized because of the possibility of late respiratory depression. During hip surgery in the elderly patient, 0.2 mg of morphine added to 12 mg of isobaric bupivacaine produced analgesia for a median duration of 24 hours, compared to the control group where analgesia was sustained for 9 hours (median).²² Prolonged pain control (±24 hours) was also obtained with 20 µg/kg of intrathecal morphine after spinal fusion.²³ In another study, patients undergoing knee arthroplasty also benefited from the administration of 300 µg of intrathecal morphine during the postoperative period.²⁴ The same results were seen in cases of laparoscopic cholecystectomy,²⁵ thoracotomy (when combined with sufentanil),²⁶ and coronary bypass surgery.²⁷

Obstetrical anesthesia

In obstetrics, spinal opioids are used alone or combined with low doses of local anesthetics for labour and delivery. They are combined with local anesthetics for caesarean sections. Many combinations have been studied for the period of labour, with satisfactory results. Fentanyl (20-25 µg), sufentanil (5-10 µg), or morphine (150 µg), added to 1.25-2.5 mg of bupivacaine represent possible combinations. One study did not show any synergy when 1.25 mg of

TABLE 3: Examples of “local anesthetic-opioid” combinations

Authors	Surgery	Bupivacaine dose	Fentanyl dose	Failures
Ben-David B ¹⁶	Arthroscopy 2 groups of 25	3 ml 0.17 % 3 ml 0.17 %	10 µg	0/25 6/25
Kang FC ¹⁸	Caesarean section 2 groups of 15	5 mg 8 mg	25 µg	0/15 0/15
Ben-David B ¹⁹	Caesarean section 2 groups of 16	5 mg 10 mg	25 µg	0/16 0/16
Ben-David B ²⁰	Hip 2 groups of 10	4 mg 10 mg	20 µg	0/10 0/10
Kuusniemi KS ²¹	Urology 4 groups of 20 Various procedures	10 mg 10 mg 7.5 mg 5 mg	25 µg 25 µg	6.3% supplemental analgesia Group not mentioned

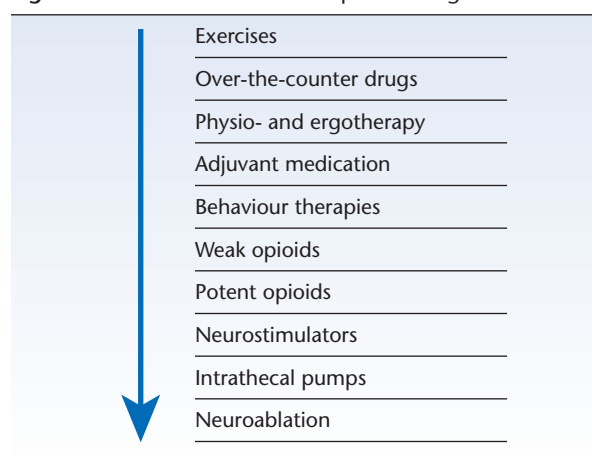
bupivacaine was added to 25 µg of fentanyl.²⁸ A recent review of the literature revealed that the use of spinal opioids during labour increases the risk of fetal bradycardia.²⁹ A meta-analysis conducted on the use of intrathecal opioids during caesarean section concluded that fentanyl (at doses ranging from 2.5 µg to 60 µg) delays the administration of post-operative analgesics by only 4 hours on average, without decreasing the total dose of medications taken during the first 6 to 24 hours. Only morphine in doses of 0.1 to 0.2 mg delays the administration of analgesics by 11 to 27 hours and decreases their subsequent use.³⁰

CHRONIC PAIN

The treatment of chronic pain is practiced mainly by anesthesiologists working within multidisciplinary teams. These anesthesiologists often tend to include invasive techniques in their global approach, such as the use of the intrathecal pump. However, this technique is indicated only when the medication administered by other routes is ineffective either because the dosage is too high or because of intolerable side effects. The intrathecal administration of opioids via a pump is therefore limited to a small number of patients. The selection of these patients is of paramount importance. Chronic pain is multidimensional and psychological assessment is essential to rule-out premorbid personalities. Pain management includes teaching many behavioural components to these patients. The indication to administer intrathecal opioids to treat chronic pain is very recent and morphine is the only drug approved by the American FDA. Some physicians question its long-term effectiveness because of the high frequency of side effects, and tolerance that necessitates escalating doses that are sometimes too high for the capacity of the pumps. Others, however, believe in its effectiveness as part of a continuum outlined in the algorithm in Figure 1.

Clinical trials

There are several ways to conduct a clinical trial in patients suffering from chronic pain. Neuraxial administration (intrathecal or epidural) of opioids can be done with a single injection or by continuous infusion. While single-dose administration is the method used most often, it cannot be recommended because of its potential placebo effect; furthermore, the patient cannot carry out activities such as climbing stairs, walking, sleeping, etc. Finally, it is difficult to anticipate the appropriate dose. A clinical trial may be conducted on ambulatory or hospitalized patients; the ambulatory setting is less costly, but there is less supervision. The duration may vary from one to several days. Fear of infection necessitates a trial of 2 to 4 days duration and some authors advocate a crossover trial with placebo and opioids.³² The following is a practical way to convert an oral dose to an intraspinal dose: 300 mg of morphine by mouth = 100 mg of

Figure 1: Continuum of chronic pain management

Modified, after Krames³¹

Table 4: Relative potency and starting intrathecal doses of commonly used opioids

Opioid	Parenteral potency (Morphine = 1)	Relative neuraxial potency (Morphine = 1)	Suggested starting intrathecal dose
Morphine	1	1	1 mg
Hydromorphone	6	2-3	0.5 mg
Methadone	1	0.5	2.5 mg
Fentanyl	100	10-15	50 µg
Sufentanil	1000	82-100	10 µg

intravenous morphine = 10 mg of peridural morphine = 1 mg of intrathecal morphine.

Different types of equipment are available for intrathecal administration. For those interested in the technical aspects, refer to Waldman.³¹

Medications

Morphine is the usual medication. It may be diluted to a maximum dose of 50 mg per cc. In cases of chronic pain, it is preferable to limit morphine to doses of 20 mg per day, although certain authors have gone as high as 60 mg per day. However, the accumulation of active metabolites can cause paradoxical hyperalgesia, allodynia, and myoclonus.³³ For this reason, it is advisable to add a co-medication when tolerance occurs. Bupivacaine and clonidine are the medications most often added, either alone or together. A dose of 8 mg of bupivacaine per day does not cause any motor block. Some studies have gone as high as 24 mg/day. For clonidine, the doses vary from 50 to 900 µg/day. With higher doses of clonidine, there is greater danger of hypotension and sedation. In general, it is better to limit the dose to approximately 300 µg/day. Morphine may be replaced by hydromorphone, which is, on average, 5 times more potent. It may be diluted to as much as 300 mg per cc.

In an American study, 95.5% of the medication administered was morphine. However, lipophilic opioids (fentanyl, sufentanil, alfentanil, and buprenorphine) alone or in combinations were also used in about 8% of cases. Compared to morphine, the accepted potency ratio for their intravenous use does not apply to intrathecal administration (Table 4). Bupivacaine was used as an adjuvant medication to morphine in 19.8% of cases. The patients in this study had a linear increase in their dose, reaching stable levels after one year. They used an average of 9.2 mg of bupivacaine per 24 hours. Medical reports reported excellent alleviation of pain in 52.4% of cases, and good alleviation in 42.9% of cases; however, this was a retrospective study.³⁴

Contraindications to the use of intrathecal opioids for chronic pain are few. They include

infection, either systemic or localized at the site of insertion of the material, or a lesion in the intraspinal space, thus preventing circulation of the cerebrospinal fluid. If there is any doubt about cerebrospinal fluid circulation, a CT scan or MRI is imperative.

CANCER PAIN

Cancer pain is successfully treated via the enteral route in 90% to 95% of cases. Palliative care teams, established in recent years, regard pain management as an important aspect of their practice. Certain cases will necessitate an invasive approach and frequently, at their request, peridural and spinal catheters are installed. The high cost of programmable pumps, the brief period of survival, and the distress these patients experience favours the use of tunneled catheters with external pumps. The infection rate in these often anergic patients is surprisingly low, ie, approximately 5%. Morphine escalation occurs more quickly than in patients with chronic pain, and opioid doses are higher.³⁵ The approach to determination of dosages is the same as for noncancerous pain.

SIDE EFFECTS AND COMPLICATIONS

Some of the side effects and complications of the intraspinal opioids, such as nausea and vomiting, hypotension, drowsiness, muscle rigidity, and early respiratory depression, are proportional to the dose and may be due to their vascular absorption. The characteristic side effects of the spinal use of opioids include pruritis, urinary retention, and late respiratory depression. These effects are not as obvious when opioids are used for chronic or cancer pain. On the other hand, certain specific side effects may be observed in these patients, such as edema of the lower limbs and certain endocrine and sexual dysfunctions. One particular side effect mentioned in the literature is a reactivation of herpes simplex labialis.

Monitoring

Monitoring is particularly important when spinal opioids are administered for acute pain, whether postoperative or obstetrical techniques

are used. Monitoring of vital signs, respiratory rate, and level of sedation is advised, as well as use of a visual analog scale to evaluate pain relief. In obstetrical practice, the fetal heart rate must also be monitored.

Nausea and vomiting

Nausea and vomiting occur in approximately 30% of cases. These effects are likely caused by cephalic migration of opioids to receptors in the area postrema.³⁶ Nausea and vomiting may be reduced with intravenous metoclopramide (10 to 20 mg), ondansetron hydrochloride (4 to 8 mg), droperidol (0.75 to 1.5 mg), or dimenhydrinate (50 to 100 mg).

Respiratory depression

The exact incidence of respiratory depression is unknown. Late respiratory depression requires observation of the patient for 4 to 6 hours with the lipophilic opioids and for over 24 hours with morphine. Respiratory depression is treated with doses of naloxone 0.1 mg IV every 1 to 2 minutes, depending on the response. An infusion of a mixture of naloxone 0.4 mg in 100 cc of saline at a flow-rate of 10 cc per hour is a good solution for prolonged respiratory depression. Episodes of respiratory depression have also been reported in neonates after epidural administration of morphine, fentanyl, or sufentanil.³⁶

Pruritis

Pruritis, the most common side effect, is likely caused by cephalic migration of opioids to the trigeminal nucleus located superficially in the medulla, where opioid receptors are found.³⁶ It may be treated with diphenhydramine hydrochloride (25 to 50 mg IV), or naloxone in microdoses of 40 µg.

Urinary retention

The precise incidence of urinary retention is unknown since many patients often have a urinary catheter. The frequency is higher when opioids are administered peridurally or intrathecally rather than via the intramuscular or intravenous route. One possible explanation is the effect of opioids on receptors in the sacral region of the spinal cord. This interaction inhibits the sacral parasympathetic system, causing muscle relaxation of the bladder, leading to urinary retention. An experiment in humans demonstrated a marked increase in bladder muscle relaxation 15 minutes after the peridural injection of 2, 4, and 10 mg of morphine that lasted for 16 hours, as compared to the intramuscular or intravenous injection of 10 mg of morphine.^{36,37} This effect can be reversed with strong doses of

naloxone, namely a bolus of 0.4 mg followed by infusion at 10 µg/kg/hour. This will significantly neutralize the analgesia.^{36,38}

Muscle rigidity

Muscle rigidity may occur after administration of opioids via the peridural or spinal routes.³⁶ However, it occurs less frequently than after intravenous administration. For an explanation of this phenomenon, refer to the article in *Anesthesiology Rounds*, August/September 2002.³⁹

Gastrointestinal motility

Spinal opioids may induce a delay in digestive transit. Two explanations are suggested for this effect. The first is systemic, implying that opioids can be active in the digestive tract, mainly in the gastric antrum and the duodenum. However, given the low doses used for spinal administration, this mechanism probably has little effect. The other mechanism involves both the medullary and periventricular cerebral sites.³⁶

Herpes simplex labialis

Reactivation of the herpes simplex labialis virus is a concern for 2 to 5 days after the intrathecal injection of opioids. This may be caused by activation of the virus located at the trigeminal nucleus where opioid receptors are also found. This hypothesis was called into question, however, by a study reporting that as many as 84% among parturients without a neuraxial injection will exhibit signs of reactivation of the virus.³⁶

Edema of the lower limbs

Edema occurs after long-term treatment for chronic or cancer pain. The incidence is unknown and probably underestimated. To some extent, support hose and diuretics can help reduce the problem, and in one study, the use of aldactone gave good results.³⁵

Endocrine and sexual dysfunction

While the incidence of sexual and endocrine dysfunction is high with chronic use of intrathecal opioids, they have only recently been investigated. Studies show a decrease in serum testosterone levels, a high incidence of hypogonadotropic hypogonadism, as well as central hypocorticism and growth hormone deficiency in approximately 13% and 17% of subjects, respectively.³⁵

Yves Veillette, MD, FRCPC, is Director of the Pain Treatment Clinic at the Maisonneuve-Rosemont Hospital in Montreal.

References

1. Pert CB, Synder SH. Opiate receptor: demonstration in nervous tissue. *Science* 1973;179:1011.
2. Atweh SF, Kuhar MJ. Autoradiographic localization of opiate receptors in rat brain. I. Spinal cord and lower medulla. *Brain Res* 1977;124:53-67.
3. Taguchi A, Sharma N, Saleem RM, et al. Selective postoperative inhibition of gastrointestinal opioid receptors. *N Engl J Med* 2001;345(13):935-40.
4. Le Bars D, Adam F. Nociceptors and mediators in acute inflammatory pain. *Ann Fr Anesth Reanim* 2002;21(4):315-35.
5. Stander S, Gunzer M, Metzger D, Luger T, Steinhoff M. Localization of micro-opioid receptor 1A on sensory nerve fibers in human skin. *Regul Pept* 2002;110(1):75-83.
6. Hughes J, Smith TW, Kosterlitz HW, Fothergill LA, Morgan BA, Morris HR. Identification of two related pentapeptides from the brain with potent opiate agonist activity. *Nature* 1975;258:577-80.
7. Yaksh TL, Rudy TA. Analgesia mediated by direct spinal action of narcotics. *Science* 1976;192:1357-58.
8. Wang JK, Nauss LA, Thomas JE. Pain relief by intrathecally applied morphine in man. *Anesthesiology* 1979;50:149.
9. Rance MJ. Multiple opiates receptors – their occurrence and significance. In: Bullingham RES, ed. *Clinics in Anaesthesiology*. Vol. 1. Philadelphia: W.B. Saunders;1983:183-199.
10. Franz D. Pharmacology of analgesic receptors. *J Pharm Care Pain Symptom Contr* 1994;2:37-38.
11. Sabbe M, Yaksh T. Pharmacology of spinal opioids. *J Pain Symptom Manage* 1990;5:191-203.
12. Maher CE, Eisenach JC, Pan HL, Xiao R, Childers SR. Chronic intrathecal morphine administration produces homologous mu receptor/G-protein desensitization specifically in spinal cord. *Brain Res* 2001;895(1-2):1-8.
13. Bonica JF. *The Management of Pain*, 2nd edition. Philadelphia, PA: Lea & Febiger; 1990:1968-69.
14. Rigler ML, Drasner K, Krejcie TC, et al. Cauda equina syndrome after continuous spinal anesthesia. *Anesth Analg* 1991;72(3):275-81.
15. Tarkkila P, Huhtala J, Tuominen M. Transient radicular irritation after spinal anaesthesia with hyperbaric 5% lignocaine. *Br J Anaesth* 1995;74(3):328-9.
16. Ben-David B, Solomon E, Levin H, Admoni H, Goldik Z. Intrathecal fentanyl with small-dose dilute bupivacaine: better anesthesia without prolonging recovery. *Anesth Analg* 1997;85(3):560-5.
17. Boucher C, Girard M, Drolet P, Grenier Y, Bergeron L, Le Truong HH. Intrathecal fentanyl does not modify the duration of spinal procaine block. *Can J Anaesth* 2001;48(5):466-9.
18. Kang FC, Tsai YC, Chang PJ, Chen TY. Subarachnoid fentanyl with diluted small-dose bupivacaine for cesarean section delivery. *Acta Anaesthesiol Sin* 1998;36(4):207-14.
19. Ben-David B, Miller G, Gavriel R, Gurevitch A. Low-dose bupivacaine-fentanyl spinal anesthesia for cesarean delivery. *Reg Anesth Pain Med* 2000;25(3):235-9.
20. Ben-David B, Frankel R, Arzumonov T, Marchevsky Y, Volpin G. Minidose bupivacaine-fentanyl spinal anesthesia for surgical repair of hip fracture in the aged. *Anesthesiology* 2000; 92(1):6-10.
21. Kuusniemi KS, Pihlajamaki KK, Pitkanen MT, Helenius HY, Kirvela OA. The use of bupivacaine and fentanyl for spinal anesthesia for urologic surgery. *Anesth Analg* 2000; 91(6):1452-6.
22. Kwan As, Lee BB, Brake T. Intrathecal morphine for post-operative analgesia in patients with fractured hips. *Hong Kong Med J* 1997;3(3):250-255.
23. Urban MK, Jules-Elysee K, Urquhart B, Cammisa FP, Boachie-Adjei O. Reduction in postoperative pain after spinal fusion with instrumentation using intrathecal morphine. *Spine* 2002;27(5):535-7.
24. Than PH, Chia YY, Lo Y, Liu K, Yang LC, Lee TH. Intrathecal bupivacaine with morphine or neostigmine for postoperative analgesia after total knee replacement surgery. *Can J Anaesth* 2001;48(6):551-6.
25. Motamed C, Bouaziz H, Franco D, Benhamou D. Analgesic effect of low-dose intrathecal morphine and bupivacaine in laparoscopic cholecystectomy. *Anaesthesia* 2000;55(2):118-24.
26. Mason N, Gondret R, Junca A, Bonnet F. Intrathecal sufentanyl and morphine for post-thoracotomy pain relief. *Br J Anaesth* 2001; 86(2):236-40.
27. Jara FM, Klush J, Kilaru V. Intrathecal morphine for off-pump coronary artery bypass patients. *Heart Surg Forum* 2001;4(1):57-60.
28. Lim EH, Sia AT, Wong K, Tan HM. Addition of bupivacaine 1.25 mg to fentanyl confers no advantage over fentanyl alone for intrathecal analgesia in early labour. *Can J Anaesth* 2002;49(1):57-61.
29. Mardirosoff C, Dumont L, Boulvain M, Tramer MR. Fetal bradycardia due to intrathecal opioids for labour analgesia: a systematic review. *BJOG* 2002;109(3): 274-81.
30. Dahl JB, Jeppesen IS, Jorgensen H, Wetterslev J, Moinicke S. Intra-operative and postoperative analgesic efficacy and adverse effects of intrathecal opioids in patients undergoing cesarean section with spinal anesthesia. *Anesthesiology* 1999;91(6):1919-27.
31. Krames ES. When all else fails: A role for Implantable Pain Management Devices. In: Waldman SD, Winnie AP, eds. *Interventional Pain Management*. Philadelphia, PA:WB Saunders;2001;58:597.
32. Doleys DM. Psychological assessment for implantable therapies. *Pain Digest* 2000;10:16-23.
33. Sjøgren P, Thunøborg LP, Christrup L, Hansen SH, Franks J. Is development of hyperalgesia, allodynia and myoclonus related to morphine metabolism during long-term utilisation? Six case histories. *Acta Anaesth Scand* 1998;42:1070-5.
34. Paice JA, Penn RD, Shott S. Intraspinal morphine for chronic pain: A retrospective multicenter study. *J Pain Symptom Manage* 1996;11:71-80.
35. Mironer YE. Neuroaxial opioid therapy. In: Tollison CD, Satterthwaite J, Tollison J, eds. *Practical Pain Management*. Philadelphia, PA: Lippincott; 2002:144.
36. Rawal N. Spinal opioids for acute pain management. In: Raj PP, ed. *Practical management of Pain*. St. Louis, MO: Mosby; 2000:689-709.
37. Rawal N, Möllefors K, Axelsson K, Lingardh G, Widman B. An experimental study of urodynamic effects of epidural morphine and a naloxone reversal. *Anesth Analg* 1983;62:641-7.
38. Rawal N, Schott U, Dahlstrom B, et al. Influence of I.V. naloxone infusion on analgesia and untoward effects of epidural morphine. *Anesthesiology* 1986;64:194-201.
39. Fortier LP. Opiates and rigidity. *Anesthesiology Rounds* 2002;1(3):1-6.

Upcoming Scientific Meetings

3-4 May 2003

Update on the Clinical Pharmacology of Opioids with Special Attention to Long-acting Drugs

Sloan-Kettering Cancer Center
New York, NY

CONTACT: Tel: 212-639-2662
Email: zp@mskcc.org

22-24 May 2003

Pain: The Silent Epidemic

Canadian Pain Society
Toronto, ON

CONTACT: Fax: 613 234-9874
Email: sfranklin@can-nurses.ca
Web site: www.canadianpainsociety.ca

Change of address notices and requests for subscriptions to *Anesthesiology Rounds* are to be sent by mail to P.O. Box 310, Station H, Montreal, Quebec H3G 2K8 or by fax to (514) 932-5114 or by e-mail to info@snellmedical.com. Please reference *Anesthesiology Rounds* in your correspondence. Undeliverable copies are to be sent to the address above.

This is an English translation of the original French article.

This publication is made possible by an educational grant from
Organon Canada Limited