

Anesthesiology
2000; 92:876-80
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Intrathecal Baclofen Is Analgesic in Patients with Chronic Pain

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INTRATHECAL infusion of baclofen is a Food and Drug Administration-approved treatment for spasticity. Although animal studies indicate that baclofen has analgesic properties when injected spinally,¹ there are few reports of intrathecal baclofen use for the treatment of pain in humans, and most of those studies have examined its use in patients with central pain associated with spinal cord injury.²⁻⁴ We have found that intrathecal baclofen provides persistent analgesia in some patients with chronic pain not associated with spasticity. The drug has been effective in multiple clinical situations when other treatments have failed or produced intolerable side effects. As in animal studies,⁵ it is effective in patients who have become tolerant to intrathecal morphine and provides analgesia at doses that do not produce motor dysfunction. Here we present a series of case reports. Table 1 provides a summary of these cases.

Case Reports

Case 1

Case 1 is a 69-yr-old man with a history of intractable left lower-extremity pain after a war-related injury that necessitated a below-knee amputation. He described his pain as a constant burning sensation over the stump with paroxysms of lancinating pain radiating from the distal portion of the stump to the knee and thigh. The intensity was rated at

a 10 using a 0-10 verbal pain scale. The patient was treated for several years with oral opioids, antidepressants, anticonvulsants, phenothiazines, muscle relaxants, peripheral nerve blocks, and a transcutaneous electric nerve stimulator. He also had a revision of the amputation and surgical neurolysis of the peroneal nerve. However, the reexploration only worsened the burning pain in the stump. The patient was referred to the pain clinic as a last option before proceeding with an above-the-knee amputation. An intrathecal morphine trial was performed, which provided 50% improvement, and the decision was made to proceed with an implantable pump. After the implantation of an intrathecal catheter and a Medtronic Synchronomed infusion pump (Minneapolis, MN), the patient required increasing doses of intrathecal morphine to maintain the initial response. The addition of bupivacaine to the infusion helped to control his pain for 1.5 yr. The intrathecal doses of the aforementioned drugs slowly escalated to 11 mg/day morphine and 3.3 mg/day bupivacaine. At these doses, the patient developed side effects that included sedation, peripheral edema, and shortness of breath. The pump was then emptied, and infusion of baclofen 50 µg/day was initiated in combination with the previous morphine dose of 11 mg/day. Within days his neuropathic pain improved, and the need for morphine decreased, allowing the eventual discontinuation of the morphine in the pump. In addition, he was better able to perform his activities of daily living, his sleep pattern improved, and his physical activity increased. Ten months after initiation of intrathecal baclofen, he was using baclofen alone at a dose of 460 µg/day with no side effects. His motor examination and deep tendon reflexes were unchanged since initiation of baclofen therapy. His pain was absent with activity and ranged from 0 to 6 at rest. The rest pain was fairly well controlled with oral gabapentin 400 mg three times per day. The more severe lancinating paroxysmal episodes of pain had completely resolved.

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Received from the Department of Anesthesiology and Critical Care Medicine, University of New Mexico School of Medicine, and the Veterans Affairs Medical Center, Albuquerque, New Mexico. Submitted for publication March 18, 1999. Accepted for publication November 3, 1999. Support was provided solely from institutional and/or departmental sources.

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Key words: Analgesia; infusion; spinal.

Case 2

Case 2 is a 71-yr-old woman referred for the treatment of intractable low back pain and neuropathic pain of the lower extremities after multiple lumbar laminectomies and fusions with bone grafts. Treatment with physical therapy, transcutaneous electric nerve stimulator, and tricyclic antidepressants had provided inadequate pain relief. High-dose oral opioids provided inadequate analgesia and intolerable side effects. She rated her pain as 9-10 on a 0-10 verbal pain scale. The patient had a continuous epidural morphine trial, using doses up to 10 mg/day, which provided 65% improvement in her pain. A Medtronic Synchronomed infusion pump with an intrathecal catheter was implanted, and the patient was started on intrathecal morphine at 1 mg/day. The patient reported marked improvement of the low back

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pain but only minimal improvement of the radicular burning pain. Bupivacaine was added to the morphine, and the infusion was slowly increased to 6.6 mg/day morphine and 0.65 mg/day bupivacaine. The pain stabilized at these doses at a level of 4-7 of a possible 10. However, she developed fluid retention, shortness of breath, peripheral edema, and sedation. An attempt to lower the infusion rate was associated with exacerbation of the pain. The patient was admitted, and the pump solution was changed to baclofen, which was begun at a dose of 50 $\mu\text{g}/\text{day}$. During the first day of baclofen therapy, her pain decreased from 7 to 4 of a possible 10, and her side effects slowly improved over the following week. Eight months later, her burning radicular pain as well as the low back pain was controlled with a combination of baclofen 210 $\mu\text{g}/\text{day}$ and morphine 2.1 mg/day. There was no subjective weakness noted by the patient, and her motor examination and reflexes were unchanged from her initial examination. Her activities of daily living were not improved because of other unrelated medical problems. She reported no side effects to the intrathecal infusion.

Case 3

Case 3 is a 44-yr-old man with cerebral palsy and a history of intractable low back pain and burning radicular pain in the left lower extremity, unrelieved by a lumbar laminectomy and fusion. Motor function and reflexes in the lower extremities were intact. He was on oral tramadol, gabapentin, nortriptyline, and high-dose sustained release oxycodone and had undergone multiple surgical procedures in an attempt to control his pain. These procedures included the implantation of three different spinal cord stimulator systems followed by multiple revisions of the epidural leads. His verbal pain score was consistently 8-9 on a scale of 0-10. The patient was admitted to the hospital, and a single intrathecal injection of 50 μg baclofen was administered. Within 3 h, the patient reported a 60% improvement in pain. A second baclofen spinal injection of 75 μg was performed 24 h later, providing complete resolution of his pain. The patient received an implanted Medtronic intrathecal infusion pump. He has remained pain-free for 7 months and is currently receiving 105 $\mu\text{g}/\text{day}$. The oral narcotics and adjuvant medications were discontinued without any increase in pain. Motor function and reflexes were unchanged compared with his preimplantation examination.

Case 4

Case 4 is 56 yr-old woman referred for the management of intractable lower-extremity pain after the development of a retroperitoneal hematoma that resulted in ischemic lumbar plexopathy. Her pain was poorly responsive to oral opioids, trazadone, or clonazepam. The patient had been implanted with a Medtronic SynchroMed infusion pump and intrathecal catheter at another institution. She was receiving intrathecal morphine at a dose of 0.3 mg/day. Her 0-10 verbal pain score ranged from 5 to 7. She could not tolerate clothes or blankets over her legs because of severe tactile allodynia. Motor examination revealed considerable lower-extremity weakness, and she was unable to ambulate without assistance. Deep tendon reflexes were absent bilaterally. The morphine infusion rate was increased over time to 0.8 mg/day without improvement in the burning pain or allodynia. However, the side effects worsened, and she became sedated, constipated, and could

not tolerate higher doses. The patient was admitted to the hospital when she complained of an increase in the pain to a score of 10 and increased weakness of the lower extremities. The pump and catheter were checked, and no displacement or malfunction was identified. The pump was emptied, and the solution was changed to baclofen. The baclofen infusion rate was initiated at 50 $\mu\text{g}/\text{day}$ and increased to 75 $\mu\text{g}/\text{day}$ on the third hospital day. The patient reported gradual improvement. By the fourth hospital day, her pain had decreased to 5 on the scale of 0-10, and her lower-extremity weakness had improved as well. Two weeks after the change to intrathecal baclofen, her pain and allodynia had decreased an estimated 75%, and her verbal pain score was 3 on the scale of 0-10. The patient has now been on intrathecal baclofen for 6 months, the infusion rate has been increased to 100 $\mu\text{g}/\text{day}$, and her allodynia has completely resolved. Her burning pain is rated at 3 on the 0-10 scale, and her subjective strength is at her normal baseline. Deep tendon reflexes are absent as they have been since the diagnosis of ischemic lumbar plexopathy. Motor function was unchanged compared with her preimplantation findings.

Case 5

Case 5 is a 50-yr-old man with a history of severe left lower-extremity pain. He received a gunshot wound to the gluteal area with injury to the sciatic nerve in 1970, with persistent pain that began immediately after the injury. He experienced mild, constant pain in the sciatic nerve distribution, rated as a 3 on a 0-10 verbal pain scale, plus severe, intermittent lancinating pain, rated as a 10. The severe pain radiated from the buttock to the foot and occurred 10-20 times per hour, each episode lasting approximately 30-40 s. Motor and sensory function in the affected limb were intact, but his left achilles and patellar reflexes were slightly reduced (1 of 4) compared with the right (2 of 4). Previous treatment included oral opioids, anticonvulsants, antidepressants, muscle relaxants, and transcutaneous electric nerve stimulator, all with minimal benefit. A spinal cord stimulator was placed 6 yr previously but failed to provide substantial relief. A trial of intrathecal morphine dramatically reduced the frequency and severity of his episodes of severe pain. A Medtronic SynchroMed intrathecal infusion pump was implanted. Initially, symptoms were well controlled on 2 mg/day intrathecal morphine. His severe pain episodes occurred four to six times per hour and were rated at 5 on the 0-10 scale. However, after 2 months, the morphine dose reached 8 mg/day, his symptoms were poorly controlled (15-20 episodes per hour, pain rating 9-10 on the 0-10 scale), and he began developing burning pain in the opposite leg. He was then treated with a combination of intrathecal morphine 2 mg/day plus bupivacaine 3.5 mg/day, which produced mild numbness in both legs but no improvement in symptoms. Discontinuation of morphine relieved the right lower-extremity pain. A trial of intrathecal baclofen, 50 μg through the side port, provided partial relief, whereas a subsequent bolus dose of 100 μg produced almost complete relief. An intrathecal baclofen infusion was initiated at 100 $\mu\text{g}/\text{day}$ with dramatic reduction in both the intensity and severity of his painful episodes. After 20 months of treatment, his symptoms remain considerably improved with 250 $\mu\text{g}/\text{day}$ baclofen. He experiences some painful episodes, but they are much less frequent (two to four episodes per hour), and are less severe (pain rating of 2 on the 0-10 scale). Motor and reflex examination have remained unchanged since baclofen infusion was initiated.

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Table 1. Summary of Pre-baclofen Treatment and Results of Intrathecal Baclofen Administration

Case No.	Prior Oral Medications	Prior IT Medications	Pre-Baclofen Pain Score (0–10)	Baclofen Initial Dose ($\mu\text{g}/\text{day}$)	Baclofen Final Dose ($\mu\text{g}/\text{day}$)	Post-Baclofen Adjunct Medications	Treatment Duration (months)	Post-Baclofen Pain Score (0–10)
1	Opioids, anticonvulsants, antidepressants, phenothiazines	Morphine, bupivacaine	5–10	50	460	Paroxetine, gabapentin	10	0–6
2	Opioids, antidepressants	Morphine, bupivacaine	7–10	50	210*	Sertralene, oxycodone	8	0–3
3	Opioids, antidepressants, tramadol, anticonvulsants	None	9–10	50	105	None	7	0–4
4	Opioids, antidepressants, anticonvulsants	Morphine	5–10	50	100	Gabapentin, trazadone	6	0–3
5	Opioids, antidepressants, anticonvulsants	Morphine, bupivacaine	9–10	100	250	None	20	2

IT = intrathecal.

* Combined with morphine, 2.1 mg/day.

Discussion

Intrathecal baclofen is antinociceptive in several experimental animal models. Wilson and Yaksh¹ and Hammond and Drower⁶ found that l-baclofen produced dose-dependent antinociceptive effects in rats using the hotplate and tail-flick tests. Antinociception was evident at doses that produced no apparent motor impairment. Similar doses were ineffective systemically. Intrathecal muscimol, a γ -aminobutyric acid (GABA)_A agonist, produced antinociception only at doses that caused some motor impairment.⁶ Intrathecal l-baclofen also produced antinociceptive effects in cats at doses devoid of motor effects.¹ In the shock titration primate model of antinociception, intrathecal l-baclofen produced profound analgesia lasting from 14 to 18 h.⁵ Baclofen was equally effective in animals made tolerant to intrathecal morphine. Dose-dependent lower-extremity flaccidity was demonstrated in some animals, but there was no comparison between the analgesic and motor-blocking doses. It is therefore unclear whether antinociception occurred in the absence of motor effects. Using the formalin test in rats, Dirig and Yaksh⁷ showed that baclofen produced dose-dependent reduction in both phase 1 and phase 2 pain behaviors at doses that had no effect on motor function. The antinociceptive effect was prevented by pretreatment with a GABA_B-specific antagonist. A similar study demonstrated that intrathecal baclofen reduced only the phase 2 pain behavior after formalin injection,⁸ suggesting that the drug blocks noxious stimulus-induced spinal sensitization.

In addition to experimental documentation of the antinociceptive effect of intrathecal baclofen, there is also evidence that intrathecal baclofen may moderate the effects of neuropathic pain. Hwang and Yaksh⁹ examined the effects of intrathecal baclofen on tactile allodynia induced by ligation of the L5/L6 nerve roots in rats (Chung model). They found that baclofen, at doses somewhat lower than those that produce antinociception, antagonized established tactile allodynia induced by nerve injury. The doses needed to reverse the allodynia produced no discernible effect on motor function. Other studies have shown that allodynia induced by an ischemic spinal cord injury is attenuated by baclofen but not by the GABA_A agonist muscimol.¹⁰

γ -Aminobutyric acid receptors regulate function of dorsal horn cells both presynaptically and postsynaptically. GABA is thought to produce presynaptic inhibition by reducing the release of neurotransmitters from primary afferent nerve terminals. It reduces neuronal activity postsynaptically by producing hyperpolarization. GABA_A receptor activation produces cell body hyperpolarization by increasing chloride ion conductance.¹¹ GABA_B receptors are linked to potassium and calcium channels by a G protein. Activation of these receptors leads to hyperpolarization through an increase in K⁺ conductance and a reduction in Ca²⁺ currents.¹² It has been proposed that in allodynic states, produced either by peripheral nerve or spinal cord injury, there is a loss of tonic inhibition of glutamate release from either primary afferent nerve terminals or from excitatory inter-

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neurons.⁹ This loss of inhibition may be related to reductions in spinal GABA levels,^{3,12} and spinal baclofen administration may restore inhibitory function.

There has been only one previous report of the analgesic effect of intrathecal baclofen in patients with pain not associated with spinal cord pathology. Vatine *et al.*¹³ reported substantial analgesia lasting 6–39 h in a series of six patients with low back pain and lumbosacral radiculopathy treated with a single injection of 250 µg baclofen. A seventh patient experienced persistent relief with the same treatment. Our series demonstrates that continuous baclofen infusion provides ongoing pain relief for prolonged periods of time for patients who do not have spasticity or spinal cord pathology. As in animal models, our patients did not experience clinically significant motor dysfunction. Intrathecal baclofen was effective in several patients who had become tolerant to intrathecal morphine. It seems to be a useful alternative or addition to continuous intrathecal opioids in patients with nociceptive, neuropathic, and central pain states.

Because the follow-up period for most of our patients has been short, it is not clear whether tolerance to intrathecal baclofen for chronic pain management will be a significant problem. In reports of the use of intrathecal baclofen for spasticity, tolerance does not seem to be a major problem. In one report, only 10 of 27 patients required dose escalation, and the increases were small.¹⁴ In another 10 patients, the dose could be reduced over time, and in 7 patients, symptoms remained minimal after the drug was discontinued.¹⁴ In a series reported by Abel and Smith,¹⁵ 3 of 23 patients experienced dose escalation to > 1,000 µg/day and eventually became unresponsive to therapy.

Compatibility of morphine plus baclofen in intrathecal pumps does not seem to be a concern. The two drugs have been shown to be compatible and stable for at least 30 days in infusion pumps at 37°C.^{16,17} Degradation products of both morphine and baclofen were detected at levels < 1% of the concentration of the parent drugs.¹⁷

The cost of intrathecal preparations of baclofen is fairly high, particularly when compared with generic or compounded preparations of preservative-free morphine and bupivacaine. On the basis of cost alone, this drug should not be considered as a first-line drug for intrathecal administration in most situations. However, a number of patients seem to experience better analgesia and fewer side effects with low doses of baclofen, which may be more cost-effective than high doses of intrathecal morphine.

These case reports suggest that intrathecal baclofen is effective in some chronic pain states that are not associated with spasticity. All of these cases involved patients who had experienced failure with multiple treatments, including intrathecal opioid administration. In none of our patients was the motor blocking effect of baclofen a clinically significant problem. Intrathecal baclofen has been demonstrated to be safe for long-term spinal administration and is approved for use in chronic spinal drug administration systems. A systematic assessment of the use of this form of therapy for patients with chronic neuropathic, nociceptive, and central pain seems warranted.

References

1. Wilson PR, Yaksh TL: Baclofen is antinociceptive in the spinal intrathecal space of animals. *Eur J Pharmacol* 1978; 51:323–30
2. Loubser PG, Akman NM: Effects of intrathecal baclofen on chronic spinal cord injury pain. *J Pain Symptom Manage* 1996; 12:241–7
3. Herman RM, D'Luzansky SC, Ippolito R: Intrathecal baclofen suppresses central pain in patients with spinal lesions. *Clin J Pain* 1992; 8:338–45
4. Middleton JW, Siddall PJ, Walker S, Molloy AR, Rutkowski SB: Intrathecal clonidine and baclofen in the management of spasticity and neuropathic pain following spinal cord injury: A case study. *Arch Phys Med Rehabil* 1996; 77:824–6
5. Yaksh TL, Reddy SVR: Studies in the primate on the analgesic effects associated with intrathecal actions of opiates, alpha-adrenergic agonists and baclofen. *ANESTHESIOLOGY* 1981; 54:451–67
6. Hammond DL, Drower EJ: Effects of intrathecally administered THIP, baclofen and muscimol on nociceptive threshold. *Eur J Pharmacol* 1984; 103:121–5
7. Dirig DM, Yaksh TL: Intrathecal baclofen and muscimol, but not midazolam, are antinociceptive using the rat-formalin model. *J Pharmacol Exp Ther* 1995; 275:219–27
8. Przesmycki K, Dzieciuch JA, Czuczwar J, Kleinrok Z: An isobolographic analysis of drug interaction between intrathecal clonidine and baclofen in the formalin test in rats. *Neuropharmacology* 1998; 37:207–14
9. Hwang JH, Yaksh TL: The effect of GABA receptor agonists on tactile allodynia in a surgically induced neuropathic pain model in the rat. *Pain* 1997; 70:15–22
10. Hao J-X, Hu X-J, Aldskogius Hm Seiger A, Weisenfeld-Hallin Z: Allodynia-like effects in rat after ischemic spinal cord injury photochemically induced by laser irradiation. *Pain* 1991; 45:175–85
11. Borman J, Hamill OP, Sakmann B: Mechanisms of anion permeability through channels gated by glycine and gamma-aminobutyric acid in mouse cultured spinal neurons. *J Physiol* 1987; 385:243–86
12. Sawynok J: GABAergic mechanisms of analgesia: An update. *Pharma Biochem Behav* 1987; 26:463–74

13. Vatine JJ, Magora F, Shochina M, Drenger M, Kriskautzky M, Magora A: Effect of intrathecal baclofen in low back pain with root compression symptoms. *Pain Clin* 1989; 2:207-17

14. Dressnandt J, Conrad B: Lasting reduction of severe spasticity after ending chronic treatment with intrathecal baclofen. *J Neurol Neurosurg Psychiatry* 1996; 60:168-73

15. Abel NA, Smith RA: Intrathecal baclofen for treatment of intrac-

table spinal spasticity. *Arch Phys Med Rehabil* 1994; 75:54-8

16. Tsui M, Lam S: Stability of intrathecal baclofen and morphine (letter). *Aust J Hosp Pharm* 1992; 22:258

17. Sitaram BR, Tsui M, Rawicki HB, Lam S, Sitaram M: Stability and compatibility of intrathecal admixtures containing baclofen and high concentrations of morphine. *Int J Pharmaceutics* 1997; 153: 13-24

Anesthesiology
2000; 92:880-2
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Pulmonary Embolism as a Consequence of Applying Sequential Compression Device on Legs in a Patient Asymptomatic of Deep Vein Thrombosis

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INTRAOPERATIVE pulmonary embolism (PE) is an uncommon complication of emergency intraabdominal surgery. Best practice recommendations for longer surgical cases include the fitting of antithrombotic leg devices such as stockings and pneumatic compression devices.^{1,2} Although these devices certainly prevent thrombosis in deep vein thrombosis (DVT)-prone surgical patients,^{1,2} we were unable to find reports of any significant complications caused by them (besides minor skin bruising, sores, *etc.*), namely, dislodgment of a pre-existing thrombus, causing a life-threatening PE. Although PE has been observed after tourniquet deflation in orthopedic surgery cases,³ we report a case of PE possibly related to pneumatic sequential compression device.

Case Report

A 56-yr-old woman who had been in bed for 2-3 days came to the emergency department with signs and symptoms of a small bowel obstruction. She had recently been diagnosed with lymphoma. The working diagnosis in this woman, who had undergone no prior abdominal surgery, was obstruction caused by a secondary deposit of tumor. Although she was in considerable abdominal pain, there was no indication of either pulmonary insufficiency or of lower-extremity swelling.

After fluid resuscitation and administration of antibiotics, the patient was taken to the operating room, where her initial vital signs and oxygen saturation (Sp_{O_2}) were within normal limits. A sequential compression device with long sleeves (Sequel model 6325; Kendall Company, Mansfield, MA) was applied to both legs as part of routine practice for any surgery lasting over 3 h. The sequential device was turned on just before the induction of anesthesia with inflation pressures around 45 mmHg. General anesthesia was induced using a rapid-sequence technique. The medications included thiopental and succinylcholine. After injection of induction agents but before insertion of an endotracheal tube, the pulse oximeter reported a near instantaneous decrease from 100% to approximately 75% (despite the administration of 100% oxygen). Her systolic blood pressure also decreased to 90 mmHg from a preanesthesia value of 130/70 mmHg. Prompt intubation, ventilation with oxygen at a fraction of inspired oxygen of 1.0 atm, and confirmation of tube placement, both by auscultation as well as by positive end-tidal carbon dioxide, did not succeed in restoring her Sp_{O_2} to the preanesthesia level. She also was noted to have high peak airway pressures (> 40 cm H_2O), a low end-tidal carbon dioxide level (approximately 22 mmHg), and Sp_{O_2} around 95%. An arterial blood gas in the operating room later revealed pH of 7.25, carbon dioxide partial pressure of 55, oxygen partial pressure of 83, and HCO_3 of 25 on 1.0 fraction of inspired oxygen, and positive end-expiratory pressure of 10 cm H_2O . Desaturation was initially attributed to an unobserved

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Received from the Departments of Anesthesia and Critical Care and Surgery, Washington University School of Medicine, St. Louis, Missouri. Submitted for publication June 18, 1999. Accepted for publication November 3, 1999. Support was provided solely from institutional and/or departmental sources.

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Key words: Pneumatic compression; prophylaxis; trauma.