Cancer pain relieved by long-term epidural morphine with permanent indwelling systems for self-administration

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Clinical trials for abatement of intractable pelvic cancer pain were conducted in two patients, each electing surgical implantation of one of two indwelling catheter systems for administration of morphine into the spinal epidural space. Both systems, one consisting of a partially indwelling Broviac catheter, and the other, completely indwelling, consisting of a morphine reservoir connected to a shunt pump and on-off Hakim valve assembly, permitted the patients to return home where they could self-administer epidural morphine. Each patient reported that 2 mg of epidural morphine provided 8 to 12 hours of pain relief at a level superior to their previous systemic narcotic medication. On a regimen of 2 mg of epidural morphine administered twice daily, both patients experienced analgesia for 6 months, unaccompanied by alterations in sensory, motor, or cognitive functioning, and with little drug tolerance reaction.

KEY WORDS • pain • spinal cord • morphine • epidural injection

The systemic narcotic dose required for palliation of severe cancer pain often leaves the patient somnolent and inactive. However, recent animal and human studies have shown that focal application of morphine in the spinal epidural or subarachnoid space results in pain abatement without depression of the central nervous system.2 4 6-8 15 18-20 This report describes two surgically implantable systems for self-administration of spinal epidural morphine, each capable of providing long-term relief of cancer pain without depression of cognitive, sensory, or motor function.

Case Reports

Case 1

The Broviac catheter* is a partially indwelling system. This system was used successfully in Case 1.

This 56-year-old man presented with intractable pain secondary to metastatic bladder carcinoma invading the left lumbosacral plexus. He was receiving Dilaudid (hydromorphone hydrochloride, 4 mg by mouth twice daily), but complained that it did not provide satisfactory relief from his suffering, while rendering him somnolent or incoherent.

A temporary epidural catheter was inserted at L2-3 and advanced to T-12 for a trial of epidural morphine administration. With 2 mg of morphine twice daily, the patient experienced a level of pain relief that was significantly greater than that provided by his regimen of Dilaudid, while allowing him to become more active. Accordingly, after considering the surgical alternatives, the patient and his family elected the placement of a permanent epidural catheter.

Implantation. On July 17, 1980, general anesthesia was induced and the patient was placed in a lateral position with the right side up. A lumbar midline incision was carried through the skin and fascia, exposing the spinous processes of L-1 and L-2. The superior portion of the L-2 process was removed, as were the interspinous and yellow ligaments, thus exposing the dura. A Holter ventricular catheter was directed cephalad in the epidural space and secured in position with the tip at approximately T11-12. A subcutaneous tunnel was made from the lumbar incision around the lateral side of the abdomen to a small subcostal incision. Through this tunnel the proximal end of an adult Broviac catheter was drawn into

* Broviac catheter manufactured by Evermed, P.O. Box 296, Medina, Washington.
This 55-year-old woman was suffering from intractable pain in the perineum secondary to pelvic carcinoma. She complained that her current regimen of pain medication dulled her senses without relieving her pain. At the time she was taking a Brompton's solution or 10 to 15 mg of intramuscular morphine every 3 hours when desired. Morphine administered through a trial epidural catheter, 2 mg twice daily, provided significantly greater pain relief than her previous analgesic regimen. Accordingly, having considered the alternative types of surgical intervention, the patient chose implantation of a completely indwelling system for self-administration of epidural morphine.

**Implantation.** The operative procedure was carried out on May 16, 1980. The epidural placement of the Holter straight catheter was identical to that described in Case 1 for the partial indwelling system. Through a second vertical incision in the lateral abdomen, a PBC 500-ml Silastic-coated blood pack was placed, containing 300 mg of morphine and 300 ml of saline. The reservoir outlet tubing was connected to a Hakim reservoir-high pressure pump shunt valve assembly, and an on-off valve overlying the iliac crest. These were joined by subcutaneous Silastic tubing to the distal end of the epidural catheter and secured in position (Fig. 2).

**Postoperative Course.** The patient learned to self-administer 2 mg of epidural morphine which provided her with satisfactory relief for a period of 8 to 12 hours. On a regimen of 2 mg of epidural morphine administered twice daily the patient went home looking forward to performing household chores and working in the garden “without being dragged down with continual pain.” This system remained in place and was effective for 7 months until her death from advancing malignancy.

**Discussion**

Clinical trials of two indwelling systems for self-administration of low-dose epidural morphine were considered justified on the basis of experimental work in animals and numerous short-term clinical trials in man.

**Animal Experiments**

Opiate receptors, which are activated endogenously by met-enkephalin,\(^{21,22}\) have been discovered autoradiographically in spinal cord laminae one and two (substantia gelatinosa).\(^{1,13}\) Morphine has also been demonstrated to activate these receptors, and has been shown to selectively inhibit the release of substance P,\(^{23}\) suppressing peripheral nociceptive input to the
Epidural morphine for pain relief

Substantia gelatinosa. Spinal segmental analgesia, which is reversible by naloxone and unaccompanied by effects on motor or sensory function, has been elicited in the rat, cat, and primate with microgram doses of morphine in the spinal subarachnoid space. 18,20,24-26

Short-Term Clinical Trials

The applicability of direct spinal morphine for pain abatement has been confirmed with short-term clinical trials. Patients suffering from pelvic cancer pain have experienced prolonged segmental analgesia with 0.5 to 1.0 mg of morphine applied to the spinal subarachnoid space.19 Subsequent short-term studies have shown that 2 to 5 mg of morphine applied to the spinal epidural space produces 6 to 24 hours of analgesia for cancer pain, acute postoperative pain, and chronic low-back pain. Pharmacological tolerance reaction to epidural morphine appears to be minimal and has been observed to be reversible by a single epidural dose of lidocaine.6

Based on the absence of opiate receptors in peripheral nerves, on the fact that xylocaine and other drugs cross the spinal dura into the cerebrospinal fluid, and on current ongoing experimental human data, we postulate that epidural morphine produces analgesia by directly activating the opiate receptors in the spinal cord.

Long-Term Clinical Trials

The success of short-term clinical trials of epidural morphine for pain control led to the design of the two systems described in this report, each of which offered the patients the benefit of long-term administration of epidural morphine at home. To avoid the risk of respiratory depression resulting from morphine reaching cervical-medullary regions, we selected patients with bilateral leg or pelvic cancer who chose a trial system for long-term epidural morphine administration in preference to a midline myelotomy or bilateral cordotomy. In both cases, adjacent colostomies or urethrostomies were not contraindications. Each patient had satisfactory long-term pain relief with 2 to 3 mg of morphine administered twice daily, and both became mentally and physically more active after stopping their high-dose systemic narcotic regimen.

The partially externalized Broviac catheter system has already been used extensively in children and adults for long-term right atrial intravenous administration of chemotherapeutic agents and hyperalimentation drugs.3,9-11,14,16,17 Even in severely immunosuppressed patients, the infection rate has been reported to be only about 8%.17 Exit tracts from indwelling Broviac catheters seal in 6 months, permitting the use of clean rather than sterile occlusive dressing and allowing for normal activity, including swimming.

A trial injection of a larger volume of fluid (10 ml rather than 2 ml) into the Broviac catheter carried metrizamide further cephalad in the epidural space, reaching up to T-4 (Fig. 3). Thus, the partially indwelling system offers the potential of producing analgesia at higher spinal levels, with the injection of additional fluid acting as a vehicle to carry morphine higher in the epidural space.

The completely indwelling system also offers the opportunity for self-administration of epidural morphine, as with the partially indwelling system, but with a potentially lower risk of infection and no wound care. Reservoir filling is required every 2 to 12 months depending on usage.

A third system, not described in the present report, consists of an implantable automatic pump reservoir which continuously infuses morphine into the epidural space at a rate of 4 to 5 ml per day. This system, demonstrated in this laboratory to be effective in dogs, is now also ready for an initial clinical trial period.

† Automatic pump reservoir manufactured by Metal Bellows Corp., Sharon, Massachusetts.
FIG. 3. Radiographic display of metrizamide distributed segmentally within the epidural space. The catheter entered the epidural space beneath the lamina of L-3 (arrow B) and passed cephalad to end adjacent to L-1 (arrow A).

Thus, it is clear that direct spinal administration of morphine offers a new and promising dimension to the therapeutic efficacy of opiates, eliminating the need for chronic systemic narcotic treatment for many types of cancer pain. Development of the two indwelling catheter systems described in this report offers patients the opportunity for self-delivery of long-term epidural morphine, allowing them to return home to their family while on an effective narcotic regimen that does not produce depression of the central nervous system and is characterized by minimal tolerance reaction. Accordingly, we believe these systems warrant further clinical trials.

References


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