Constant infusion of morphine for intractable cancer pain using an implanted pump

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In the past, pain control for chronic pain syndromes using narcotic infusion has been carried out primarily via the intrathecal (subarachnoid) route. This report presents one of the first large series of terminally ill cancer patients with intractable pain treated with continuous epidural morphine infusions by means of implanted pumps and epidural spinal catheters. The purpose of the study was to demonstrate that the epidural route is effective with minimal complications, and that screening with temporary epidural catheter infusions results in a high rate of subsequent pain relief. A multidisciplinary team (neurosurgeon, anesthesiologists, psychiatrists, oncologists, and nurse clinicians) evaluated and treated all of the patients studied. Percutaneous placement of temporary epidural catheters for a trial assessment was performed by the anesthesiologists. Pain evaluations were conducted independently by psychiatrists using both verbal and visual analog scales. From 1982 to 1988, 41 (59.4%) of 69 patients evaluated for eligibility experienced good pain control during trial assessment and were subsequently implanted with Infusaid infusion pumps. Preinfusion pain analog values were 8.6 ± 0.3 and postimplantation values at 1 month were 3.8 ± 0.4 (p < 0.001). Over this same 1-month period, requirements of systemic morphine equivalents decreased by 79.3% with epidural infusions as compared to preinfusion requirements (p < 0.001). There were no instances of epidural scarring, respiratory depression, epidural infections, meningitis, or catheter blockage. One patient developed apparent drug tolerance and three patients required further catheter manipulations. This series strongly suggests that significant reductions in cancer pain can be obtained with few complications and a low morphine tolerance rate using chronic epidural morphine infusion. Anesthesiology and psychiatry input, along with temporary catheter infusion screening and quantitative pain evaluations using analog scales, are essential.

KEY WORDS - cancer - pain - implantable pump - epidural infusion - morphine

THE infusion of narcotics in terminally ill cancer patients with intractable pain is a technique that has been increasingly utilized in the past 8 years. The major route for these infusions has been intrathecal (subarachnoid).2-5,6,8,9,14,20-23,25,27,29 This form of therapy, however, carries the risks of meningitis, catheter occlusion, and potential nerve root or spinal cord injury. Detailed information about the efficacy and complication rates with the epidural infusion of morphine has previously been lacking.

This report presents one of the largest series of cancer patients with intractable pain who have been treated with the epidural infusion of morphine using implanted pumps. The purpose of this study was twofold. First, the study was undertaken to demonstrate whether the epidural route is a valid clinical alternative that can be effective in pain control with minimal complications and with significant ease of catheter placement. Second, with the initial screening of eligible patients by temporary epidural catheters and external infusion pumps, the study was designed to show whether the patients selected for pump implantation could experience high rates of pain relief.

Clinical Material and Methods

Patient Eligibility and Population

Between April 1, 1982, and August 1, 1988, a consecutive series of patients at the Cleveland Clinic Foundation were treated with epidural morphine infusions. To be eligible for admission into the study, the patients had to meet the following criteria: 1) have terminal cancer with midline and/or bilateral lower body pain; 2) have been ineligible for resection of any tumor; 3) have had inadequate pain control by oral, rectal, and/or intravenous preparations of narcotics without significant side effects; 4) have had an expected survival time of at least 1 month; 5) have either received maximal radiation therapy to the pain sites or have such extensive disease that radiation therapy was not practical; 6) have...
no contraindications to the epidural placement of a catheter (for example, previous spine operations with epidural scarring, infection in the vertebral column, or spinal column instability); and 7) have no significant psychiatric illness that would interfere with the treatment. The patients were evaluated and treated by a multidisciplinary team comprised of a neurosurgeon, psychiatrist, anesthesiologist, and nurse clinician. All patients were evaluated by all members of the team.

Over the 6-year study period, 69 patients were entered into the study. The patients ranged in age from 28 to 83 years (mean ± standard deviation: 57.1 ± 2.3 years). The types of cancer in these patients were as follows: rectum-colon (65%), endometrium/cervix (11%), bladder (5%), breast (3%), prostate (3%), stomach (3%), renal (3%), pancreas (3%), and skin (melanoma, 3%). The pain affected the pelvis, back, and legs in 43% of cases, the rectum in 22%, the perineum and genital region in 16%, the pelvis and abdomen in 11%, the low back only in 5%, and the chest wall bilaterally in 3% (Table 1).

Preoperative Evaluation

The evaluation of pain was a very important aspect of this study. Two separate pain scales, a visual analog scale, and a verbal analog scale, were utilized. The visual analog scale consisted of a horizontal bar measuring 10 cm in length. Each patient was asked to place a mark along this bar, where the left end represented no pain and the right represented the worst imaginable pain. The verbal scale consisted of asking the patient to rate the pain on a scale of 0 to 10, where 0 represented no pain and 10 the worst imaginable pain.

Once a patient was judged by the team to have met all the eligibility criteria listed above, a percutaneous temporary epidural infusion catheter was placed by anesthesiology pain therapist. The patient was then tested for 2 to 4 days with continuous morphine infusion through the catheter from a conventional external infusion pump. Pain control was evaluated by analog scales during this period. Adequate control was defined during this time by at least a 30% reduction in pain analog values and epidural morphine doses of less than 40 mg/day. The epidural morphine infusion rate for temporary infusion was initially based upon the patient’s body weight.

Pump Implantation and Initial Dosage

If a patient was judged to have had significant pain relief from infusion via the temporary catheter (at least 30% pain relief with infusions of < 40 mg/day), then a permanent epidural catheter and infusion pump were implanted.* The technique consisted of percutaneous (guided under fluoroscopy through a Tuohy needle) or open (through a small laminotomy) epidural placement of the permanent infusion catheter. The catheter entered the epidural space at the L1–2 level with the catheter tip at T11–12, and was placed through a subcutaneous tunnel to the anterior upper quadrant of the abdomen. The catheter was then connected to a constant-rate infusion pump implanted subcutaneously at the same site.

The pump was filled and primed in the operating room with a preservative-free morphine solution. The concentration of the solution was adjusted to provide a morphine rate (in mg/hr) that was two-thirds of the rate delivered by the temporary epidural catheter.

Patient Follow-Up Monitoring

Each patient was followed by a home health care nurse trained to refill the pumps as needed (approximately every 2 weeks). All patients were then evaluated at 1 month after implantation and every 3 months thereafter until the death of the patient or removal of the pump. At each follow-up examination the following were recorded: 1) the patient’s infusion rate of morphine; 2) pain severity (based on visual and/or verbal analog pain scales); and 3) any complications or problems related to the pump. Apparent drug tolerance was defined as rapidly escalating epidural morphine requirements that could not be met within the limitations of the infusion pump.

Statistical Considerations

Statistical evaluations were initially performed using comparisons in different groups of the mean values ± standard error of the mean. Wilcoxon signed-rank tests were used to determine if changes in data collected before and after the start of the epidural morphine infusions were significantly different from zero.

Results

Of the 69 patients entering the study, 41 (59.4%) patients experienced significant pain relief with infusions through the temporary catheters, and subsequently received permanent implantation of catheters.

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* Catheter and pump supplied with the Model 400 implantable pump set manufactured by Infusaid Corp., Norwood, Massachusetts.
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and infusion pumps. Of these 41 patients, 37 (90.2%) were evaluable for this report. The remaining four patients were alive but unavailable for follow-up review longer than 1 month after implantation. The mean survival time for patients after the operation was 7.1 ± 1.2 months (range 1 to 27 months).

Before epidural morphine infusion, patients were receiving, in systemic (oral, rectal, and/or intravenous) narcotics, morphine intravenous equivalents averaging 77.7 ± 19.1 mg/day. After 1 month of epidural morphine infusion, the systemic narcotic dose was 16.1 ± 3.6 mg morphine intravenous equivalents/day (p < 0.001). After 9 months of infusion, the systemic dose was 27.9 ± 11.0 mg/day. The mean epidural dose after 1 month of infusion was 20.7 ± 2.6 mg/day rising to 49.3 ± 9.9 mg/day after 9 months of infusion. The pain analog scales showed a decrease from 8.6 ± 0.3 before epidural morphine infusion to 3.8 ± 0.4 after 1 month of epidural morphine infusion (p < 0.001) (Fig. 1). Of the 41 patients receiving implanted epidural catheters and pumps, 87.1%, 81.0%, and 81.2% were judged to have satisfactory pain relief at 1, 3, and 6 months after pump implantation, respectively, based upon a minimum of 30% decrease in pain analog values as compared to preinfusion values.

There were no instances of respiratory depression, epidural infections, catheter blockage, or clinically apparent epidural scarring (Table 2). Potential scarring was defined by presence of partial or complete catheter obstruction and/or evidence of epidural compression by a mass at the distal part of the catheter. Apparent tolerance to the narcotic epidural infusion (based upon a need for significantly escalating epidural morphine doses that could not be met within the limitations of the infusion pump) developed in one patient after 24 months of infusion. This patient, however, had very extensive metastatic disease involving the entire pelvis. She responded to steroids and additional radiotherapy with marked pain relief and experienced adequate subsequent pain control with continued epidural morphine infusion.

One patient developed a superficial wound infection requiring removal of the implanted pump and permanent catheter. Two other patients developed superficial wound infections not requiring removal of the pump or catheter. A subcutaneous tunnel for the catheter tubing, which was too superficial, resulted in skin necrosis in one patient. There was catheter migration with subsequent leak of infusion solution in one patient; catheter migrations not requiring any intervention occurred in three other patients. The infusion pump itself delivered a constant infusion rate that was lower than expected in one patient; this was easily corrected with an appropriate change in the concentration of the morphine solution in the pump. Voiding disturbances of minor clinical significance were noted in three patients.

Discussion

Previous Studies of Intrathecal Narcotic Infusions

The intrathecal (subarachnoid) infusion of narcotics in terminal illnesses has been studied in numerous reports using morphine. These evaluations have studied the efficacy (pain control), complications, and development of drug tolerance or tachyphylaxis. It would appear that 80% to 90% of the patients were reported to have “excellent” pain relief with the need for minimal or no systemic analgesics. Unfortunately, however, very few of these studies have actually quantitated pain relief by means of a pain scale.

Complications have included: catheter and meningitis infections; catheter blockage; spinal pain during catheter injections; nausea, vomiting, and diaphoresis; respiratory depression; and urinary retention. In most series, these problems have shown an incidence of 5% to 15%. An additional problem noted in each series was “treatment failure;” these were patients in whom the intrathecal catheters were implanted but in whom no significant pain relief was experienced.

The development of drug tolerance is a more difficult problem to characterize and to treat. Usually, in cancer patients, drug tolerance is functionally defined as the...
need for rapidly escalating drug doses to control pain that cannot be met because of the limitations of the infusion pump.²²,²³ Others believe that, in cancer patients, the progression of the disease alone accounts for the dose requirements.⁶,²⁹ In most patients receiving intrathecal infusions there is some dose escalation, perhaps up to two times the initial dose within 9 months after catheter placement. However, severe dose escalation resulting in pain that cannot be controlled by infusion devices occurs in approximately 2% to 5% of all patients.²²,²³,²⁵,²⁷ This situation is usually considered as drug “tolerance.” A slope of 0.8 or greater on a graph of intraspinal morphine dose (y axis) versus time after infusion start (x axis) has also been used as evidence of rapid tolerance development.²³ Drug “holidays” (temporary discontinuation of the infusion) and intrathecal infusions of anesthetic agents such as xylocaine and other drugs such as clonidine have been reported as treatments for this problem.⁸,¹⁰,¹⁸

**Previous Studies of Epidural Narcotic Infusions**

Epidural morphine infusions have been studied by others for cancer pain treatment³-⁵,¹¹,¹⁵,¹⁶,¹⁹,²³,²⁵-²⁸ and non-neoplastic chronic pain.¹,⁵,¹²,¹⁷ Many such reports have included the use of substances other than morphine for epidural infusions.⁵,⁷,¹³,²⁴ In most series of spinal infusions, the majority of patients have received intrathecal infusions with only a small minority receiving epidural infusions. Most of these techniques of epidural delivery were also performed through bolus injections into either subcutaneous reservoirs or catheters tunneled subcutaneously and then externalized. In general, these limited studies have shown pain control figures comparable to those obtained with intrathecal infusions. Few of the studies, however, have quantitated actual pain control with the consistent use of pain scales.

It is often stated that infusion via the epidural route results in a higher complication rate;² however, a previous survey of the recent literature has indicated a lower complication rate with epidural as compared to intrathecal infusions.²⁷ The real potential complication rate of epidural infusions has been difficult to evaluate because of the small size of previously reported series. Furthermore, an assessment of the benefits of this form of infusion is not possible due to the absence of large series of patients receiving epidural morphine infusions via constant subcutaneous (implanted) infusion.

**Multidisciplinary Evaluation and Screening of Cancer Patients**

The present study contributes one of the largest series of consecutive patients treated with epidural narcotic infusions via subcutaneous continuous infusion pumps. The patients in this study have been well-characterized by means of: 1) the specific and rather extensive eligibility criteria; 2) thorough predmission psychiatric evaluation of patients including screening for previous personality disturbances and previous evidence of drug abuse potential; and 3) thorough evaluation of each patient during the infusion by means of pain scales (verbal and visual), systemic narcotic use, and epidural morphine dosage. This study also contributes data on the consistent use of pain scales both before and at multiple times after implantation of the catheter and pump. Figure 1, in its composite comparison of systemic narcotic usage, epidural morphine dosage, and pain scale rating, exemplifies this contribution.

This series also emphasizes the importance of screening patients with temporary infusion catheters in order to exclude those patients most unlikely to benefit from the permanent catheter and pump. In fact, this study is unique among previous reports of spinal narcotic infusions (intrathecal or epidural) because of the large number of patients, consistent use of specific pain scales, screening of patients by means of temporary catheters and infusions, and length of the patient follow-up period.

**Long-Term Efficacy and Safety of Epidural Narcotic Infusions**

Using the techniques and tools described above, the efficacy of the morphine epidural infusions in the control of cancer pain was quite impressive. The systemic narcotic requirements in these patients decreased from a preoperative average of 77.7 to 19.1 mg/day morphine intravenous equivalents after 1 month of epidural infusion. In the same manner, mean pain scale scores showed a similarly dramatic decrease from 8.6 (pre-epidural infusion) to 3.8 (after 1 month of epidural infusion). Mean epidural morphine dosages ranged from 20.7 to 49.3 mg/day 1 to 9 months after pump implantation, respectively, as compared to reports of dosages using 5 to 30 mg/day with long-term intrathecal infusions.²,²⁵,²⁷ The significance of these effects is emphasized by the fact that all of the patients in the present study had severe pain that could not be adequately controlled by oral and/or rectal narcotic preparations prior to pump implantation.

Anecdotally, there have been concerns about the possible complication rate of epidural infusions. These concerns resulted, in part, from the previous lack of a large series of patients treated with such infusions. The present study, however, showed a very low complication rate with only one superficial wound infection. Also of significance was the absence of catheter blockage or epidural infection. The Infusaid constant-rate infusion system was also found to be quite reliable, and the use of the infusion pump, as opposed to bolus injections, was probably a significant factor in the prevention of catheter blockage due to epidural scar formation. The use of a temporary external catheter and a separate permanent implanted catheter also helped to minimize the risk of infection.

The mean length of survival in this study was slightly greater than 7 months. However, in the application of epidural or intrathecal infusions in terminally ill cancer patients, this is actually a longer period of survival than...
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reported in most previous studies. Hence, based upon this study, there appears to be minimal cause for concern of drug tolerance with epidural morphine infusion in the terminally ill cancer patient.

Relative Roles of Epidural and Intrathecal Narcotic Infusions

This study was designed to determine the efficacy and safety of constant epidural morphine infusions in a relatively large group of terminally ill cancer patients. It cannot, of course, compare the merits of intrathecal and epidural infusions. It would appear that the epidural infusion of morphine is a valid alternative to the intrathecal infusion. This is based upon the results of this series which involved a large number of patients who were followed for a significantly long survival period. The study also emphasized the importance of a thorough evaluation, both before infusion (psychiatric evaluation and testing with temporary catheter infusions) and during infusion (consistent use of specific pain scales and documentation of all narcotic use).

Determination of the preferred route, intrathecal or epidural, seems to depend upon the expertise available in a particular hospital or practice. Having shown epidural infusions to be an acceptable alternative, the next study that awaits design and completion is a randomized comparison of these two routes in a large group of patients for a definitive evaluation of relative efficacy and complication rates.

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References


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