Chronic intrathecal morphine for intractable pain

RICHARD D. PENN, M.D., AND JUDITH A. PAICE, R.N., M.S.
Department of Neurosurgery, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois

Forty-three patients with intractable pain received intrathecal morphine delivered by implanted continuous-infusion (Infusaid) or programmable (Medtronic) devices. In 35 patients the pain was due to cancer, and eight patients had chronic nonmalignant pain. The origin of the nonmalignant pain included lumbar arachnoiditis, multiple sclerosis, severe osteoporosis resulting in a thoracic compression fracture, and intractable pain as a consequence of cancer therapy in individuals cured of their disease. Twenty-eight (80%) of the patients with cancer-related pain experienced excellent or good relief. Side effects were rare. Tolerance occurred infrequently and could be managed effectively. The results of this study support earlier studies on the application of chronic intrathecal morphine for intractable cancer pain. These findings also indicate that, in carefully selected patients, nonmalignant pain may be managed satisfactorily with this technique.

KEY WORDS implantable drug device □9 intrathecal morphine □9 pain

NEUROSURGICAL procedures are often the last resort for patients suffering from intractable cancer pain. Unfortunately, many of these operations have limited effectiveness and are inappropriately invasive for debilitated patients. Furthermore, the pain is frequently midline or bilateral, and burning or boring in character — the most difficult to manage surgically. The discovery of opiate receptors in the spinal cord and the subsequent demonstration that pain could be relieved by epidural or intrathecal spinal morphine has suggested a new alternative. Chronic infusion of morphine via infusion systems has been investigated in several centers and the initial results have been encouraging.1-3,5-14 The key clinical questions that remain to be answered are: how this technique should be used in the overall management of cancer pain, what role it may have in treating benign pain, and whether the incidence of tolerance with long-term infusion is significant.

In the past 4 years, we have implanted drug pumps in 43 patients with pain due to a wide variety of causes. On the basis of this experience we believe that certain types of cancer pain should be treated earlier and more aggressively with intrathecal morphine, that tolerance occurs but is rarely a cause for failure of pain control, and that some types of benign pain can be successfully managed by the technique.

Clinical Material and Methods

As of July 1, 1986, drug-administration devices have been implanted in our institute in 43 patients, 24 with an Infusaid constant-flow pump and 19 with a Medtronic programmable device.* In 35 patients the pain was due to cancer. These were selected using the following criteria: 1) life expectancy of greater than a few months; 2) inability to adequately control pain with systemic narcotics or antidepressant or anti-inflammatory drugs; 3) location of the pain below the midcervical dermatomes; and 4) inappropriateness of neurosurgical procedures for pain relief.

Eight of the 43 patients had severe pain that was not controlled by oral narcotics. Two of these patients had been treated and cured of cancer, but had complications leading to intractable and disabling pain: one had vault necrosis secondary to radiation implants and bilateral lumbar plexus pain, and the other had herpes zoster in the distribution of the fourth thoracic dermatome. Four patients with pain of benign origin had back and leg pain due to lumbar arachnoiditis. The diagnosis was made by myelography. These patients had been treated for “failed back syndrome” with antidepressant drugs and physical therapy. By the time of referral they were receiving oral or intramuscular narcotics and still had significant pain limiting their activities of daily living. Psychometric or psychiatric evaluations revealed depression secondary to pain and the inability to work, but there was no underlying psychopathology. The seventh patient had multiple sclerosis as well as inter-

* Constant-flow pump manufactured by Shiley-Infusaid Inc., Norwood, Massachusetts; programmable pump manufactured by Medtronic, Inc., Minneapolis, Minnesota.
vertebral disc disease, and suffered from severe leg spasms and leg pain. The final patient had a thoracic compression fracture due to osteoporosis, and had been bedridden because of pain. Oral codeine, while partly relieving her pain, caused drowsiness and respiratory depression, complicating her long-standing obstructive lung disease. The patients with benign pain are included in this report only if they have received 6 months or more of intraspinal morphine.

The details of our implantation technique and pump technology have been described in a previous article. A screening procedure using epidural morphine is used on each patient. A percutaneous epidural catheter is placed at the dermatome level of the pain and attached to an external pump. Morphine, 0.1 mg/cc, is infused continuously and the dose is increased at 12- to 24-hour intervals until pain relief is reported. Objective signs of pain control are considered most important — that is, a marked decrease in systemic narcotics required and an improvement in activities of daily living — can the patient feed himself, dress, sit, or walk better? Testing may last up to 5 days, until it is clear that a good response is achieved. Only after such careful screening should a permanent implant be proposed. After consent is obtained from the Rush Human Investigation Committee and Food and Drug Administration for an exemption to use an investigational new drug and device, the Medtronic programmable drug administration device or the Infusaid constant-flow pump is implanted under local anesthesia. The pump is attached to a lumbar subarachnoid catheter. Initially, some catheters were placed epidurally, but all recent infusions have been intrathecal in order to reduce the dose of morphine and the systemic side effects.

Results

The clinical results in the 35 patients with cancer pain are shown in Table 1. The grading scale is the same as that employed previously. It combines subjective pain reports, objective changes in daily living, and oral narcotic usage for an overall score. The scale is as follows:

- Excellent: Subjective pain ratings decreased to 0–3 (on a scale of 0–10, 10 being severe pain), greater than 50% reduction of oral narcotics, and significant increase in daily activities.
- Good: Subjective pain in the 4–6 range, less than a 50% decrease in oral narcotics, and some improvement in activities of daily living.
- Poor: Subjective pain ratings in the 7–10 range, only slight decreases in oral narcotics, and little change in activities.
- Failure: No pain relief, continuing need for oral narcotics, and no change in activities.

A patient had to meet all three criteria to be placed in a particular group; thus, if a patient had a reduction in oral narcotics, a subjective pain of 6, but no improvement in activities, this was graded as a poor response. Based on this scale, 28 (80%) of 35 patients with cancer pain had a good or excellent response to intrathecal morphine infusion (Table 1). One patient was dropped from the study at his request when his new Infusaid pump did not function properly and would have required replacement. He is not included in the analysis. The mean number of treatment months will eventually be longer, since some patients are still alive and have continued to have good or excellent pain relief.

In retrospect, the three patients who failed to respond to intrathecal implantation had equivocal responses to the trial of epidural morphine. Their native languages were not English, and poor communication resulted in poor assessments. In three of the four patients with poor responses, unusually high doses of oral or intravenous narcotics had been used. The epidural trial dosages were high, and the actual intrathecal morphine needed for initial pain control via the pump were correspondingly high (20 mg of morphine/day or higher). Rapid deterioration in drug effect occurred over several weeks, and good pain relief could not be achieved again even by increasing the intrathecal morphine by 50% to 100%.

No significant morbidity or mortality has been associated with pump implantation or chronic morphine infusion. Transient urinary retention occurred at the initiation of intrathecal morphine in several male patients, but cleared after a few days. No respiratory depression, itching, mental confusion, or nausea was recorded. In fact, the most gratifying aspect of the treatment was that patients became much more alert and less depressed as the oral narcotics were decreased. Nerve root or spinal cord symptoms were not seen, even at the highest dosages (50 to 100 mg/day). The one patient who developed root symptoms of electrical pains in her legs and muscle spasms had a lumbar epidural metastasis. These symptoms cleared completely with

<table>
<thead>
<tr>
<th>Factor</th>
<th>Type of Pain</th>
<th>Cases</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>clinical grade*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>excellent</td>
<td>Cancer</td>
<td>17</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Benign</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>good</td>
<td></td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>poor</td>
<td></td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>failure</td>
<td></td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>total</td>
<td></td>
<td>35</td>
<td>8</td>
</tr>
<tr>
<td>follow-up period (mos)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total</td>
<td></td>
<td>189</td>
<td>173</td>
</tr>
<tr>
<td>mean</td>
<td></td>
<td>5.4</td>
<td>21</td>
</tr>
<tr>
<td>average increase in dose</td>
<td></td>
<td>2.4</td>
<td>3.1</td>
</tr>
</tbody>
</table>


J. Neurosurg. / Volume 67 / August, 1987
decompression surgery. Her severe burning rectal pain could be completely controlled by intrathecal morphine even in the postoperative period. In the last few weeks of the cancer patients’ lives, when they were bedridden and cachetic, many complained of generalized aching and discomfort which did not respond to oral or intrathecal medication. This discomfort was not related to the dose of intrathecal morphine.

The first trial of Medtronic programmable devices was marred by failures in four of nine units. These device problems have been overcome in a new model, and the 12 implanted pumps have worked properly. Two Infusaid devices failed: in one a gradual slowing from 2 to 0.5 cc/day was noted over 1 month due to clogging of the metal tubing within the pump, and in the other stoppage of flow occurred immediately after implantation, but the cause was never determined. Several catheters kinked and stopped morphine delivery, which had to be corrected, but with experience and thicker-walled catheters this complication has not been observed in the past 2 years. No intrathecal or pump pocket infections were seen. Cerebrospinal fluid leaked into the pocket in several instances, but this problem slowly resolved in all but one patient, in whom a reoperation was required to close the lumbar sacral fascia at the catheter site.

Tolerance to morphine was difficult to judge. Many of the patients required increasing doses of intraspinal narcotics. Typically, the dose would have doubled by the time the patient died (usually 3 to 9 months after implantation of the delivery system). Some patients required little or no increase, and in a few the dose was decreased. More rapid increases (up to four to 10 times the original dose) were rare, and usually good pain control could be maintained. Only two patients had escalating dose requirements that could not be met by the drug delivery devices. One required a marked increase in morphine within 6 weeks, and the other after 18 months. The latter patient was taken off morphine for 1 week, while a local intrathecal anesthetic was given and percutaneous cordotomy was performed. Morphine was then restarted and gave excellent relief at one-fifth the previous dose. He continued pain-free on this dose until he died at home 6 weeks later.

The eight patients with pain of benign origin are listed in Table 2, with the distribution and character of their pain. They had no operative or intrathecal drug-related complications. All patients have had good or excellent pain relief using the same scale as for the cancer pain group and have been followed for at least 6 months. A few brief clinical points about these patients should be made. The patient with herpes zoster had an epidural catheter placed at the T-4 level of involvement and receives bolus injections via the pump every 8 hours. Only after 18 months of treatment could the morphine dose be decreased; now it is two-thirds of the original amount needed for pain control.

The longest continuous intrathecal infusion (over 46 months) has been experienced by the patient with radiation necrosis (Case 1, Table 2). Her dose of intrathecal morphine has increased from 3 to 30 mg/day. Each increase was in response to a new complication (she has fractured both femurs and her pelvis). After each increase in dose her pain control has been excellent. The patient with multiple sclerosis (Case 4) was given morphine to control spasm in his legs. His back pain was a secondary problem; however, it was significantly relieved with the morphine infusion. He had been maintained on the same dose of morphine for 1 year with good pain control and no spasms until he had further deterioration in motor function due to progression of the multiple sclerosis. At that point the dose of morphine was increased 150% to help control pain.

Four patients with arachnoiditis (Cases 5 to 8) have

---

**TABLE 2**

Clinical summary in eight patients with benign-origin pain*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Cause of Pain</th>
<th>Morphine (mos)</th>
<th>Results of Treatment</th>
<th>Morphine (mg/day)</th>
<th>Location of Pain</th>
<th>Type of Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65, F</td>
<td>radiation, lumbar plexus</td>
<td>52</td>
<td>excellent</td>
<td>3</td>
<td>30</td>
<td>vaginal</td>
</tr>
<tr>
<td>2</td>
<td>41, M</td>
<td>herpes zoster at T-4</td>
<td>28</td>
<td>excellent</td>
<td>30†</td>
<td>20†</td>
<td>chest wall</td>
</tr>
<tr>
<td>3</td>
<td>69, F</td>
<td>thoracic compression fracture</td>
<td>7</td>
<td>excellent</td>
<td>1</td>
<td>1</td>
<td>midline, thoracic</td>
</tr>
<tr>
<td>4</td>
<td>71, M</td>
<td>multiple sclerosis, spasticity, arachnoiditis</td>
<td>26</td>
<td>excellent</td>
<td>2.2</td>
<td>7.5</td>
<td>midline, back, radicular 1.5–S1</td>
</tr>
<tr>
<td>5</td>
<td>46, M</td>
<td>arachnoiditis</td>
<td>36</td>
<td>good</td>
<td>26†</td>
<td>26†</td>
<td>midline, back, buttock, calf</td>
</tr>
<tr>
<td>6</td>
<td>58, M</td>
<td>arachnoiditis</td>
<td>8</td>
<td>good</td>
<td>4</td>
<td>13</td>
<td>midline, back, both legs</td>
</tr>
<tr>
<td>7</td>
<td>43, M</td>
<td>arachnoiditis</td>
<td>9</td>
<td>good</td>
<td>1</td>
<td>2</td>
<td>midline, back, l leg primarily leg pain</td>
</tr>
<tr>
<td>8</td>
<td>33, M</td>
<td>arachnoiditis</td>
<td>7</td>
<td>good</td>
<td>5</td>
<td>21</td>
<td>radicular sharp</td>
</tr>
</tbody>
</table>

* For a description of the grading scale see text. These results were sustained until death or the end of the study.
† In these patients, catheters were placed epidurally.
Chronic intrathecal morphine for intractable pain

all improved in ambulation, had 50% or more reductions in oral narcotics, and report pain scores in the 4 to 6 range. Two are self-employed and work 3 to 7 hours per day, and another is looking for work as a security guard, but has been rejected because he has had back surgery. The fourth is unable to return to his previous work as a laborer. One patient increased his dose significantly over the first 3 months, but has now stabilized for 3 months at this higher level. Another has required a more gradual increase over 6 months to maintain his good response and may need to be withdrawn from morphine therapy in the future if this trend continues.

Discussion

Since all the cancer patients in our study failed to obtain pain control with conventional drug treatment and none were candidates for percutaneous cordotomy, the good results of chronic intraspinal morphine in more than two-thirds of them is a most gratifying finding. The benefits of pain control are combined with the reduction in narcosis due to systemic narcotics, so the patient is more alert, often less depressed, and more easily managed at home. The experience of other investigators is similar, whether the spinal morphine is given by drug pump, a percutaneous filled reservoir, or an epidural catheter. The major concern has been how rapidly drug tolerance might occur. Animal experiments have suggested that significant problems would occur within a week; however, our experience is quite different. Only two of our 43 patients developed a requirement for morphine which outstripped the ability of the pump to give it. Most of the cancer patients needed two or more times the initial dose over the course of their illness. This did not result in any central side effects and the pain could be satisfactorily managed. In one of our patients with a rapidly escalating dose, a 1-week period off morphine allowed resumption at a lower dose. He was treated by intrathecal bupivacaine and percutaneous cordotomy, and could be again managed satisfactorily with intrathecal morphine at a much lower dose. Whether such withdrawal periods are the best way to manage these situations remains to be seen.

The failures in this series are as important as the successes. When the screening procedures were not followed or were interpreted incorrectly, the result was uniformly unsatisfactory. The several poor responses after initially good results suggest a different cause of failure in these patients. In each case very high oral or intravenous doses of morphine were being given prior to implantation. It is possible that the spinal opiate receptors were nearly saturated by the high systemic levels, or that those individuals with high systemic doses are the ones who have the most tolerance. On the other hand, several patients at similarly high systemic doses did well on intrathecal morphine for many months. The factors that differentiate these two groups of patients are unclear at present. If the poor results are due to true tolerance, then tolerance developed in five of 43 patients.

The finding that cancer pain can be alleviated in many patients for 6 months or longer suggests that an earlier application of this method is warranted. This is particularly true for patients who are narcotized by relatively low doses of systemic narcotics. The choice between drowsiness or pain can be avoided by intrathecal delivery of morphine. The expense of the technique also means that it should not be used as a last resort in patients who are likely to die soon; in such patients, external pumps seem more appropriate.

The most surprising finding in our study was that patients with severe pain of benign origin could be managed satisfactorily with chronic epidural or intrathecal morphine for periods of 6 months or longer. Coombs and his coworkers reported that all five of their patients with arachnoiditis did poorly with chronic epidural morphine, which has discouraged other trials; however, a recent publication by Auld et al. is much more optimistic. Over two-thirds of their patients had a good-to-excellent response for up to 2 years of treatment, a result quite similar to that found in our cancer patients. The eight patients in our study with pain of benign origin have all done well, but it must be emphasized that they were carefully selected and screened with 3 to 5 days of epidural morphine delivery in the hospital. None of the four exclusively arachnoiditis patients has had better than a good response. On the other hand, two of these patients had returned to part-time work, and the others have made gains in activities of daily living. In managing these patients, a pain-free state was never suggested as a goal, and the dosage of morphine has been maintained at moderate levels without marked escalations whenever possible. The major benefit to these patients has been the reduction of systemic narcotics and their central effects. These encouraging results should be interpreted with considerable skepticism until a much larger series of patients has been followed for many years. There is a widespread reluctance to give narcotics to patients with pain of benign origin. On the other hand, if intrathecal morphine is useful in managing the most difficult cases, it would be unfortunate to dismiss it out of hand because it necessitates chronic use. Intrathecal morphine does not lead to addiction, nor are there withdrawal effects if it is stopped. The issue does not concern chronic narcotic use, but whether the gains are sufficient to employ this expensive and continuous technique. Nonnarcotic medications like somatostatin 14, calcitonin, or clonidine have been reported to relieve pain and may provide an alternative to the opiates. At this early stage, it is not known which is the best intrathecal drug for chronic-pain patients.

Acknowledgments

The authors thank the Departments of Anesthesia, Medical Oncology, and Gynecological Oncology at Rush-Presbyterian-St. Luke’s Medical Center for their active participation and for the referral of their patients to this study.
References


Manuscript received September 29, 1986. Accepted in final form February 2, 1987.

Address reprint requests to: Richard D. Penn, M.D., Department of Neurosurgery, Rush-Presbyterian-St. Luke's Medical Center, Rush Medical College, 1753 West Congress Parkway, Chicago, Illinois 60612.