Long-term pain relief produced by intrathecal morphine infusion in 53 patients

BURTON M. ONOFrio, M.D., AND TONY L. YAKSH, PH.D.

Department of Neurologic Surgery, Mayo Clinic, Rochester, Minnesota

The present report details the characteristics of the analgesic effects of morphine administered chronically by infusion pumps implanted in 53 patients suffering from terminal metastatic disease. The median postimplant survival time in these patients was 4 months. Patients (mean age 58 years) were characterized according to the duration of pain before pump implantation (mean 16 months), prior consumption of systemic opioids (mean one to six daily analgesic equivalents of morphine), and their response to a trial intrathecal dose of morphine (1 to 2 mg). The median infusion dose at 2 weeks was 3.8 mg/day. The analgesic index, calculated as (quality of pain relief x duration of pain relief in hours)/morphine dose in mg, that was observed after the trial dose of morphine was determined for each patient. A close correlation was observed between the acute (2-week) infusion dose necessary to produce pain relief and the analgesic index such that the infusion dose = -8.0 x log (analgesic index) + 17.1. By 16 weeks, the mean spinal morphine dose for the group had increased by a factor of about 2.5; however, significant variation in the close incrementation was documented. The maximum increase was observed in patients with a low analgesic index, and this rapid incrementation was usually correlated with an unsatisfactory overall outcome. Evidence that long-term infusion continues to yield analgesia was evidenced in six cases where there was an unanticipated loss of drug infusion and a corresponding increase in parenteral narcotic consumption. These data indicate the long-term efficacy and safety of spinal opioid infusion in patients with terminal cancer, and emphasize the advantage of assessing the sensitivity of the patient to spinal opioids by a standardized trial injection prior to pump placement as a prognostic indication of outcome.

KEY WORDS • intrathecal morphine • cancer pain • pain • pump infusion • drug delivery

MORPHINE, with an action limited to opioid receptors in the human spinal cord, can evoke a powerful and relatively selective alteration in the processing of pain information.15,36 The utility of spinal morphine for the management of chronic pain has been demonstrated by repeated bolus administration of opioids into the epidural or intrathecal space.2,3,13,21,25,44,48 The use of a chronic, totally implantable, delivery system offers two advantages. It permits the periodic administration of agents into the spinal space without the need for an external port and, theoretically, the lack of repeated bolus injection limits the development of tolerance. Since its first use,11,27 a number of reports have documented the therapeutic effects produced by such intrathecal and epidural administration.6,8,15,19,22,29,30,45,47

Assessment of the efficacy of spinally infused morphine is difficult because of the diversity of patient histories and variations of the disease states in each individual. The majority of reports suggest a three- to fivefold increase in dose requirements over intervals ranging from 3 to 30 weeks,11,15,26,36 with occasional reports emphasizing an acute and rapid incrementation in dose.10,42 A previous retrospective survey of 163 patients treated by 19 physicians indicated a wide diversity in the tendency of patients to require incrementation over time of the infused intrathecal dose of morphine.57

The present series consisted of 53 systematically studied patients suffering from terminal cancer who displayed a pain syndrome sensitive to parenteral narcotics. For reasons related to inadequate management of the pain at narcotic doses due to unacceptable side effects, these patients were referred as candidates to receive an implanted chronic intrathecal infusion system. The results of the analysis of patients receiving such pumps between 1981 and 1988 and their outcomes are reported.
Pain relief produced by intrathecal morphine

Clinical Material and Methods

Patient Population

Initial criteria for patients to be admitted to this series were: 1) malignant disease was present for which palliative therapy only was prescribed; 2) the pain secondary to the disease state and/or to irradiation or operative procedures performed to treat the malignant disease was not adequately altered by the use of oral or intramuscular narcotics without unacceptable side effects (such as somnolence or depression); 3) the metastatic disease was not subject to a specific peripheral lesion (for example, neuraxis) or central lesion (for example, unilateral chordectomy), or the patient refused to accept such an iatrogenic alternative; 4) anticipated survival periods were in excess of 3 months; and 5) there was no evidence of systemic infection. Patients meeting these criteria received at least one diagnostic injection of preservative-free intrathecal morphine sulfate (0.75 to 2.0 mg) in a volume of 0.5 to 2.0 ml. Patients showing at least a fair response for a minimum of 6 hours were deemed to be appropriate subjects for implantation of a chronic infusion pump.

Pump Placement

Eight patients (Cases 1 to 8) underwent a midthoracic one-segment laminectomy under general anesthesia, and a Silastic catheter was introduced caudally and intrathecally; an attempt was made to achieve a watertight dural closure around the catheter. It was apparent from this early experience that, in this patient population, inanition and cachexia favored wound problems including infection, cerebrospinal fluid (CSF) collections along the catheter and pump sites, and displacement of intrathecal catheters. Of the final 45 patients, 43 underwent pump implantation in the lateral decubitus position with use of a local anesthetic agent while 3 cm of lumbar fascia was exposed over two contiguous midlumbar spinous processes. A No. 18 thin-walled Touhy needle was introduced into the lumbar subarachnoid space while an intraoperative C-arm intensifier was used to assure midline needle placement. A Portex catheter was introduced through the Touhy needle. A purse-string suture placed in the lumbar fascia around the needle was secured around the catheter after the needle was withdrawn, leaving the catheter anchored in the subarachnoid space. No CSF extravasation was seen subsequently in any patient; however, catheter withdrawal remained a problem in six patients. A further modification utilizing a Silastic stent as the catheter exited from the subarachnoid space was required. The subarachnoid catheter was subcutaneously passed subcutaneously from the back to the abdominal wound and telescoped into the Silastic catheter extending from the pump, leaving a small redundant loop of catheter beneath the pump to compensate for postoperative flexion and extension torso movement.

A single 1.5-mg morphine dose was placed via the side port of the pump and barbotaged into the lumbar subarachnoid space to prove catheter continuity and patency and afford immediate postoperative pain control. If extensive postirradiation changes of the abdominal wall or exteriorized ureteral or bowel stomata precluded a suitable pump site, then general anesthesia was used for subrectoral pump placement. The intraspinal catheter was still introduced by the Touhy needle technique.

Infusion System

The Infusaid 100 pump was implanted in Cases 1 to 8. Subsequently, all patients received the model 400 pump with a side port. This feature permitted verification of continued subarachnoid catheter placement, retrieval of CSF, and subsequent myelography in the case of progressive malignant peridural disease. These pumps initially delivered 2 to 3.5 ml/day. The reliability and factors governing stability of the infusion systems have been discussed elsewhere.28

Drug

Preservative-free morphine sulfate was used in these studies. Solutions for infusion were prepared by the hospital pharmacy and sterilized by filtration.

Patient Protocol

After being deemed acceptable for pump infusion, patients were counseled as to the possible benefits, limitations, and risks of pump placement. It was stressed that the pump would not likely provide better relief than that experienced during the acute bolus trial. Moreover, with prolonged treatment there might be a decrement in pain control due to drug tolerance or disease progression; both factors presenting real unknowns. Patients with high-grade or total subarachnoid blocks were excluded from consideration of pump therapy. During the postoperative phase and all subsequent periods, patients were given access to ancillary oral narcotics as needed.

Typically, the initial drug concentrations infused were between 3.0 and 6.0 mg/day. Postoperative inpatient hospitalization averaged 3 days. This period verified the adequacy of early pain relief, initiated ambulation where possible, and allowed for observation and treatment of mild nausea, vomiting, and pruritis. The patients were routinely examined at the time of the first pump refill, 17 to 28 days postoperatively, to assess wound healing and adequacy of pain control. In most
cases, the patients' local physicians were instructed in pump refilling and subsequently accomplished this task.

**Analysis of Results**

**Parenteral Narcotic Use.** The amount and identity of all parenteral narcotics consumed before and after the initiation of infusion was determined. To permit comparison between different drug regimens, the levels of the respective agents were converted and expressed as the daily analgesic equivalents of morphine (DAEM). This conversion was calculated based on the amount of drug required to produce an effect of six doses of 10 mg of morphine intramuscularly (for example, a daily analgesic concentration of morphine). Equivalency factors for other narcotics were based on those previously reported.17

**Analgesic Index.** To estimate the degree of pain relief produced by the trial dose of spinal morphine, an analgesic index (AI) was calculated according to the formula: AI = (duration of pain relief in hours × magnitude of relief)/morphine dose in mg. The magnitude of pain relief, as judged by the patient, was weighed according to the scores: 0 = none; 1 = mild/fair; 2 = good; and 3 = excellent.

**Mobility.** Functional mobility was assessed for the patient's pre- and postinfusion status and scored numerically as follows: 1 = bedridden at home or in a hospital setting, requiring significant care levels; 2 = walks sparingly, sits, and is capable of limited personal care; 3 = ambulatory and is self-sufficient as to care.

**Overall Outcome.** On the basis of post hoc examination of patient records, interviews with the patient's relatives, and the perceived satisfaction by the treating physician, the degree of satisfaction received by the patient during the course of the infusion was defined on the basis of the categoric assignments: 0 = none; 1 = fair; 2 = good; and 3 = excellent. This assessment of outcome was made independent of the levels of spinal and parenteral drug dosing.

**Statistical Data**

Population statistics are presented as the mean ± standard error of the mean and as the median with both the absolute range (range) and the values corresponding to lower and upper quartiles (L/U Q). Comparisons between groups (for example, analgesic index as a function of age < 60 years vs. > 60 years) were carried out using a Kruskal-Wallis nonparametric

### TABLE 1

**Summary of patient characteristics**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of cases</td>
<td>24</td>
<td>29</td>
<td>53</td>
</tr>
<tr>
<td>age (yrs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SEM</td>
<td>62.3 ± 1.7</td>
<td>55.2 ± 2.4</td>
<td>58.4 ± 1.6</td>
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<tr>
<td>median</td>
<td>57</td>
<td>64</td>
<td>62</td>
</tr>
<tr>
<td>range</td>
<td>24–71</td>
<td>33–83</td>
<td>24–83</td>
</tr>
<tr>
<td>L/U Q</td>
<td>45–65</td>
<td>52–66</td>
<td>50–66</td>
</tr>
<tr>
<td>primary pain duration (mos)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SEM</td>
<td>14.0 ± 2.4</td>
<td>17.8 ± 7.3</td>
<td>16.1 ± 4.1</td>
</tr>
<tr>
<td>median</td>
<td>9</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>range</td>
<td>1–36</td>
<td>2–216</td>
<td>1–216</td>
</tr>
<tr>
<td>L/U Q</td>
<td>4–18</td>
<td>3–12</td>
<td>4–13</td>
</tr>
<tr>
<td>preinfusion DAEM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SEM</td>
<td>1.6 ± 0.3</td>
<td>1.5 ± 0.2</td>
<td>1.6 ± 0.2</td>
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<tr>
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<td>1</td>
<td>1</td>
</tr>
<tr>
<td>range</td>
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<td>0.1–5</td>
<td>0.1–5</td>
</tr>
<tr>
<td>L/U Q</td>
<td>1–2</td>
<td>0.6–1.8</td>
<td>1–2</td>
</tr>
<tr>
<td>preinfusion pain duration (wks)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SEM</td>
<td>37.3 ± 8.1</td>
<td>18.7 ± 3.6</td>
<td>27.1 ± 4.3</td>
</tr>
<tr>
<td>median</td>
<td>18</td>
<td>9</td>
<td>16</td>
</tr>
<tr>
<td>range</td>
<td>1–153</td>
<td>1–93</td>
<td>1–153</td>
</tr>
<tr>
<td>L/U Q</td>
<td>13–37</td>
<td>6–22</td>
<td>8–25</td>
</tr>
</tbody>
</table>

* SEM = standard error of the mean; L/U Q = lower and upper quartile of the range; DAEM = daily analgesic equivalent of morphine.

### TABLE 2

**Summary of patient characteristics and outcome according to disease entity**

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>No. of Cases</th>
<th>Prior Pain Duration (mos)</th>
<th>Preinfusion DAEM*</th>
<th>Analytic Index</th>
<th>Duration of Infusion (wks)</th>
<th>Daily Frequency of Drug Use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Range</td>
<td>Median</td>
<td>Range</td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>colon</td>
<td>9</td>
<td>12</td>
<td>6–30</td>
<td>1.0</td>
<td>0.1–4.0</td>
<td>47</td>
</tr>
<tr>
<td>pancreas</td>
<td>8</td>
<td>6</td>
<td>1–36</td>
<td>1.0</td>
<td>0.5–5.0</td>
<td>39</td>
</tr>
<tr>
<td>rectal</td>
<td>6</td>
<td>12</td>
<td>3–36</td>
<td>1.5</td>
<td>0.3–2.5</td>
<td>42</td>
</tr>
<tr>
<td>cervical/uterine</td>
<td>6</td>
<td>13</td>
<td>2–26</td>
<td>1.6</td>
<td>1.0–3.9</td>
<td>33</td>
</tr>
<tr>
<td>lung</td>
<td>5</td>
<td>9</td>
<td>3–40</td>
<td>0.9</td>
<td>0.2–2.7</td>
<td>54</td>
</tr>
<tr>
<td>renal</td>
<td>5</td>
<td>9</td>
<td>2–13</td>
<td>1.0</td>
<td>1.0–2.0</td>
<td>44</td>
</tr>
<tr>
<td>chondroma/osteoma</td>
<td>4</td>
<td>7</td>
<td>2–24</td>
<td>1.9</td>
<td>1.5–3.6</td>
<td>20</td>
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<tr>
<td>prostate</td>
<td>3</td>
<td>9</td>
<td>3–12</td>
<td>1.0</td>
<td>0.3–1.0</td>
<td>54</td>
</tr>
<tr>
<td>breast</td>
<td>3</td>
<td>36</td>
<td>5–216</td>
<td>1.0</td>
<td>0.3–1.5</td>
<td>24</td>
</tr>
<tr>
<td>bladder</td>
<td>1</td>
<td>7</td>
<td>—</td>
<td>3.7</td>
<td>—</td>
<td>24</td>
</tr>
<tr>
<td>indiffrent/unknown</td>
<td>1</td>
<td>2</td>
<td>—</td>
<td>1.8</td>
<td>—</td>
<td>19</td>
</tr>
<tr>
<td>gallbladder</td>
<td>1</td>
<td>30</td>
<td>—</td>
<td>1.0</td>
<td>—</td>
<td>18</td>
</tr>
<tr>
<td>esophageal/neck</td>
<td>1</td>
<td>3</td>
<td>—</td>
<td>1.5</td>
<td>—</td>
<td>72</td>
</tr>
<tr>
<td>overall group</td>
<td>53</td>
<td>9</td>
<td>1–126</td>
<td>1.0</td>
<td>0.1–5.0</td>
<td>33</td>
</tr>
</tbody>
</table>

* DAEM = daily analgesic equivalent of morphine.
Pain relief produced by intrathecal morphine analysis. For repeated measures of interval data (for example, levels of systemic narcotic consumption before vs. after drug infusion) a paired t-test was employed. Differences that reached the p < 0.05 (two-tailed) level of significance were deemed statistically significant.

**Results**

**Patient Population**

The 53 patients (24 men and 29 women) receiving pumps for the management of pain had a median age of 62 years (Table 1). Table 2 presents the distribution frequency of the primary metastatic diseases. Examination of the distribution of the primary pain pattern in the 53 patients at the time of pump placement revealed the following data: 17 had pain in the cervical and thoracic vertebral levels and 34 suffered pain in the lumbar, sacral and coccygeal dermatomes. Two patients had pain referrals concurrently above and including the lumbar segments. The majority of patients displayed bilateral pain distribution. Thirty-two of the 53 patients were essentially nonambulatory.

All patients had been undergoing active pain management at the time of referral, with a median period of treatment with narcotics before pump placement of 4 months. Tables 1 and 2 present the level of systemic narcotic consumption at the time of referral as a function of gender and disease state. As noted previously, inadequate relief was achieved at these doses, and higher levels of parenteral narcotics were not typically employed to avoid side effects unacceptable to the patient.

**Effects of Preinfusion Intrathecal Morphine Trial**

All patients with an implanted spinal infusion system received a trial dosing with a probe dose of intrathecal morphine (median 1.0 mg; range 0.5 to 2.0 mg). In the patients referred for pump placement, computation of the analgesic index revealed a prominent analgesic effect which varied from fair to excellent and lasted for periods from 6 to 48 hours. Figure 1 plots the relationship between the analgesic index and age, mobility status, preinfusion DAEM, and preimplantation pain duration. There were no statistically significant associations (Kruskal-Wallis analysis: p > 0.10).

**Continuous Spinal Morphine Infusion Studies**

**Acute Effects.** Figure 2 presents the levels by week of the daily dose of morphine given spinally and the

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**Fig. 1.** Analgesic index of patients arranged as a function of age (≤ 60 and > 60 years of age at time of infusion); preinfusion pain duration (≤ 6 and > 6 months), preinfusion mobility (1 = bedridden; 2 = sitting/walks sparingly; and 3 = ambulatory); and preinfusion daily analgesic equivalents of morphine (DAEM, ≤ 1.0 vs. > 1.0). Patients are designated in two groups: with good or poor outcomes. No statistically significant correlation was observed between any of the variables and either the analgesic index or outcome. See text for further discussion.

**Fig. 2.** Upper: Number of patients receiving intrathecal (I.T.) morphine infusion as a function of time (weeks). Center: Daily intrathecal infusion dose of morphine sulfate plotted versus time of infusion in weeks. Solid line = mean; dotted line = ± standard error of the mean (SEM). Lower: Daily analgesic equivalents of morphine plotted versus time of infusion in weeks. Solid line = mean; dotted line = ± SEM.
daily analgesic equivalents of parenteral narcotics. Following the initiation of morphine infusion, the median starting infusion concentration was assessed frequently and increased at minimum intervals of 3 to 5 days to permit stabilization of spinal concentrations. At 2 weeks, the median infusion concentration for all patients was 3.8 mg/day (L/U Q: 3.3 to 5.1 mg/day).

The analgesic efficacy of chronically infused spinal morphine was indicated by several indices. First, as shown in Fig. 3 during the 3- to 6-week period following initiation of infusion, 10 of 21 patients who had a mobility score of 1, and nine of 12 patients with mobility scores of 2 showed an improvement of at least one category secondary to improved pain management. Second, based on the consumption of parenteral opiates made by the patient in the absence of pain relief, it can be seen that the average DAEM consumption fell from 1.6 ± 0.2 prior to infusion to 0.8 ± 0.2 at 2 weeks following infusion (p < 0.05). No evidence of withdrawal was observed after the initiation of the infusion and the acute reduction in systemic dose.

All patients with successful pain management, as evidenced by intake at 2 weeks of 0.3 DAEM or less (that is, statistically less than preinfusion systemic opioid consumption; p < 0.01), were pooled and the regression of the intrathecal infusion dose on the log of the analgesic index was determined: intrathecal dose (mg) = -8.01 x log (analgesic index) ± 17.1. Both the slope of the regression line and the correlation coefficient (r = 0.74) were found to be statistically significant (p < 0.05).

Chronic Effects. The concentration of spinal drug administered was variably and progressively incremented in most patients. There was also a fluctuation in DAEM (Fig. 2). Thus, by Week 16, the intrathecal infusion concentration had risen to 7.8 ± 2.2 mg/day. As the increase over time also reflected an acute change in the population constituency because of mortality, we particularly studied the group of patients who survived in excess of 16 weeks after pump implantation. In those patients, the daily infusion dose rose from 3.7 ± 0.3 mg/day in the 2nd week to 9.5 ± 2.1 mg/day by Week 16. The DAEM rose from 0.6 ± 0.1 in Week 2 to 2.1 ± 1.1 in Week 16. These increases were statistically significant (paired t-test, p < 0.05) (Fig. 4).

A third index of drug effect was the overall assessment of outcome. As noted, assignment of outcome status was made independent of the infusion concentration or the DAEM requirements of the patient. This assignment was based only on the perceived quality of life enjoyed by the patient as judged by the physician, patient, and family. Of the 51 patients receiving morphine infusion for a period in excess of 4 weeks, 34 (67%) were defined as having good or excellent results. The remainder were considered to have overall poor to only fair outcomes. Consideration of the 26 patients whose infusion period exceeded 16 weeks revealed a similar percentage (65%).

In an effort to determine if there was any correlation between preinfusion parameters and outcome, the statistical relationship was assessed between outcome for 53 patients and a number of variables including age and preinfusion mobility status. Prior duration of pain or the level of parenteral opioid consumption at the time of implementation were examined. Chi-squared
Pain relief produced by intrathecal morphine

**FIG. 5.** Increase in the daily spinal infusion dose at 16 weeks expressed as a ratio of the levels at Week 2 (upper) and the daily analgesic equivalents of morphine (DAEM) at Week 16 expressed as a ratio of the preinfusion DAEM (lower). These data are plotted as a function of the log of the analgesic index. The regressions observed with each line were statistically significant.

**FIG. 6.** Daily analgesic equivalents of morphine (DAEM, solid line) and spinal infusion dose (mg/day, broken line) preceding (P) and as a function of time (weeks) after the initiation of spinal morphine infusion at time 0 for Cases 1, 5, 41, 30, and 9, respectively. M = male, F = female/age in years.

Analysis revealed no significant association (p > 0.10). The distributions of such parameters as a function of the analgesic index are presented in Fig. 1. In two patients with pain specifically due to brachial plexus involvement uniformly poor long-term outcomes were noted.

As shown in Fig. 5, a significant regression of the ratio increase on both infusion concentration and DAEM was observed. Thus, based on these observations, overall outcome varied directly and the incrementation in spinal and systemic dose varied inversely with the preinfusion response of the patient to a bolus dose of intrathecal morphine.

**Effects of Withdrawal of Spinal Infusion on Pain Behavior**

Miscalculation of pump refill dates led to an inadvertent empty pump syndrome (recurrent severe pain) in five cases (Fig. 6). A check on the pump reservoir would typically reveal it to be empty. Following refill, the oral narcotic consumption would fall to previous levels over the ensuing 24- to 48-hour period. In a single case (Fig. 7), a 65-year-old man showed progressive incrementation in the dose of spinally infused morphine over a 2-year period, with highly satisfactory pain relief. On or around the 118th week, the patient suffered a fall and subsequently began to complain of extensive
pain and displayed an elevated DAEM. It was assumed that the increased pain occurred secondary to the injury; however, corresponding increases in intrathecal infusions from 14 to 27 mg/day did not result in satisfactory results. The patency of the pump was checked in the 126th week and it was revealed that the catheter had become dislocated. Replacement of the catheter resulted in a prompt reduction in pain and a corresponding reduction in DAEM.

**Pathology**

Autopsy was carried out in two instances. At the time of autopsy the patients had been receiving infusions for 26 and 130 weeks, respectively, with the morphine concentration at time of death being 8 and 24 mg/day, respectively. In both cases, the catheter was observed to be lying freely in the subarachnoid space with no evidence of scarring, tethering, or investment. Histological examination at the light microscopic level of the spinal cord in the vicinity of the catheter tip revealed no evidence of any inflammatory response, thickening of the meninges, loss of cells, or demyelination.

**Discussion**

The Patient

Included in this study were individuals suffering from terminal cancer with median survival times of about 4 to 6 months. Initially, they were all sensitive to systemic opioids and remained sensitive except that, at effective doses, physiological and psychological side effects were expressed which the patient found unacceptable.

Based on several independent quantitative indices, including reductions in adjunctive analgesic therapy, increases in mobility, and final overall outcomes, intrathecal morphine administered continuously by chronically placed pumps can yield clinically relevant and statistically significant reductions in the patient's pain state. The recurrence of pain, as indicated by an unpredicted and acute increase in drug self-administration when the pump was emptied or disconnected unexpectedly, emphasizes the sustained contribution of the infused morphine to the analgesic state of the patient.

The second characteristic of this patient population with pump implantation is that all displayed a significant analgesic response to a trial administration of intrathecal morphine. In patients who showed at least a minimum response to trial morphine as measured by the analgesic index, a prominent correlation was observed between the effect of chronic morphine and their trial dose response.

**Preinfusion Morphine Sensitivity: The Analgesic Index**

The analgesic index is conceptually a reflection of the efficacy of the drug in each particular patient. Under the most appropriate circumstances, all patients would receive the same probe dose (that is, 1 mg). This was not, however, the case in the present series. Analysis of the data revealed that normalizing probe dose data to determine the “hours × quality/mg” equation yielded a clear and statistically significant association with: 1) the initial concentration of morphine necessary to yield an effect sufficient to preclude the need for supplemental systemic doses, and 2) the degree of dose incrementation by 16 weeks. Thus, in a patient in whom 1 mg of spinal morphine yielded excellent pain relief for 12 hours (12 × 3 = 36), the predicted infusion dose at 2 weeks would be approximately 4.6 mg/day, based on the analgesic index and the regression equation presented previously.

**Infusion Dose Incrementation**

The spinal opioid increase at 16 weeks (a nominal interval chosen because of the significant number of patients remaining at that time point to permit a reasonably powerful statistical analysis) appears clearly correlated with the magnitude of the response evoked by the probe morphine injection. The response to probe morphine did not statistically correlate with either the preinfusion DAEM or the preinfusion pain duration. These results are in contrast to previous reports in which the morphine concentration necessary for analgesia was increased in animals26 and patients25 with significant prior exposure to systemic opiates. Failure to see a significant correlation in these studies does not mean that there is no cross tolerance between systemic and spinal morphine.

The failure in the present work to observe withdrawal symptoms upon initiation of infusion and reduction in systemic dosing is in contrast to results in several previous reports39,40 in which such signs were observed. This difference may lie in the particular nature of the pain state or in the fact that all patients tended to retain a low systemic narcotic consumption and this may have been adequate to suppress the appearance of withdrawal symptoms.

The increases in spinal infusion doses necessary over time may reflect three phenomena: pharmacokinetic or pharmacodynamic mechanisms or changes in the pain state. First, the progressive reduction in drug effect might be representative of changes in drug distribution. Evidence for the development of diffusion barriers with epidural infusions has been presented in animals41 and it is becoming increasingly appreciated that changes in the epidural space can alter extradural transfer of drug.35 With the intrathecal route, however, formation in man of such sheaths has not been evident in this study.

Second, at the concentrations of drug employed in these and other clinical studies, spinal morphine probably yields its effect by virtue of an interaction with μ opioid receptors.55,56 Chronic occupation of opioid receptors has been shown to be associated with a reduction in effect from changes in receptor number,32,38 and/or receptor coupling.57,58 Studies employing chronic spinal infusion paradigms in animal models33,37 have shown...
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significant rightward shifts in the analgesic dose-response curves of intrathecally administered opioids. Thus, removal of the opioid for periods between 7 and 14 days results in significant recovery of drug efficacy in animals, and a similar period holds for man although this has not been systematically examined.

Finally, it is clear that increasing the intensity of a somatic stimulus by tumor burden results in a rightward shift in the intrathecal opioid dose-response curves in animal models. Also, progressive involvement of nerve roots may give rise to alterations in the substrate by which pain is encoded in the central nervous system, and such pain substrates may not be opioid-sensitive. Thus, dysesthetic pain is clearly distinguishable from somatic pain in that it is evoked by $\alpha\beta$ (vs. $\alpha$ and $\delta$) primary afferents and it is relatively insensitive to opioids. Recent animal studies have indeed shown that such spinally mediated hyperalgesia can have a unique pharmacology which is relatively refractory to spinal opioid agonists.

Toxicology of Long-Term Spinally Administered Morphine

Animal studies with repeated bolus intrathecal administration of morphine for periods of 5 to 7 days in the cat, rat, and dog (Sabbe, et al: unpublished data) at concentrations approximating 10 to 20 mg/ml or chronic infusion in rodents for 7 days of up to 6 $\mu$g/ $\mu$l/hr for 7 days failed to induce any evidence of motor or sensory deficit. A previous retrospective survey of patients with terminal cancer revealed no evidence of irreversible loss of function with over 10 patient years of morphine infusion at concentrations ranging from 8 to 10 mg/ml. Although less extensive, experiences with the intrathecal bolus administration of up to 10 to 15 mg or infusion of morphine at concentrations approaching its absolute solubility have not been reported to lead to functional loss. Coombs and colleagues did note some mild degeneration of the dorsal columns, but this could have been attributable to the mechanical effects of the catheter or to the extensive involvement of the nerve roots secondary to the metastatic process or chemotherapeutic drugs. In the present study, neither patient studied at autopsy after 38 and 130 weeks of infusion, after receiving concentrations as high as 8 and 24 mg/day, showed histological or gross pathological changes. These data jointly point to the large margin of safety with regard to tissue toxicity for even supramaximal morphine concentrations.

Based on the above safety ratio, provided no side effect develops from the increased drug concentration (such as somnolence or nausea), dose incrementation itself is not an untoward event. However, at elevated concentrations, an anomalous tactile hyperesthesia has been described in animals and man. This phenomenon is thought to be strychnine-like and is not mediated by an opioid receptor. Such a phenomenon was not observed in the present studies; however, in our first patient, removal of the morphine after long periods of infusion was found to diminish the reported pain state.

The possibility of alternative agents for spinal infusion is clearly an important future direction. Limited work with the $\delta$-preferring opioid agonist d-Ala$^2$-d-Leu$^5$-enkephalin has shown favorable results. On the basis of extensive animal studies, this agent has the advantage of showing minimal cross tolerance to $\mu$ opioids. It has been shown that $\alpha_2$-agonists are also analgesically efficacious in animals and man, as with $\delta$-agonists, there is no cross tolerance with morphine. Other receptor-selective systems have also been identified. Moreover, the growing appreciation of the role of drug efficacy and the size of the spare receptor pool associated with the spinal effects of a given drug suggests that a systemic examination of $\mu$ opioid agonists other than morphine may be therapeutically valuable. It is an important point to note, however, that the spinal use of novel drugs in man must be considered only after adequate toxicology testing has been completed.

Conclusions

Based on the above analysis, it appears certain that long-term infusions of opioids can modulate pain generated by a variety of stimuli. The recurrence of pain that was observed when morphine infusion ceased either by inadvertent pump emptying or catheter disconnection, clearly emphasizes the sustaining nature of the spinal opioid effect. The ongoing incrementation in dose may result from pharmacodynamic changes in drug action (such as receptor tolerance) as well as progressive increases in the magnitude of the pain stimulus, and/or (in the extreme) the involvement of spinal substrates which are relatively insensitive to opioids. These studies also emphasize the probable benefits in pretesting spinal opioid sensitivity to define the probable acute response of the patient to spinal infusions and to suggest the probable outcome to be anticipated from long-term administration.

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B. M. Onofrio and T. L. Yaksh
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Address reprint requests to: Burton M. Onofrio, M.D., Department of Neurologic Surgery, Mayo Clinic, Rochester, Minnesota 55905.