Intrathecal and intraventricular morphine for pain in cancer patients: initial study

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Intractable pain in six cancer patients was treated with lumbar intrathecal morphine (two patients) and intraventricular morphine (four patients). Daily percutaneous injections of morphine through Ommaya reservoirs were made. Initially, 1 mg of lumbar intrathecal morphine resulted in pain relief for 10 to 14 hours, and 2.5 to 4.0 mg of intraventricular morphine gave relief for 12 to 24 hours. This treatment was continued for 3 to 7 months in three of the adults. Morphine requirements gradually increased. Side effects were minimal, and there were no complications.

KEY WORDS: cancer • intrathecal morphine • intraventricular morphine • pain relief

Recently, Kuhar and associates have identified opiate receptors in the brain and spinal cord of rats, monkeys, and humans. Opiate receptor density is generally low in the cerebral cortex, but receptor density is greater deeper in the hemispheres, near the corpus callosum. The amygdala, caudate, putamen, medial thalamus, and habenular nuclei have a high density of receptors. The bulk of the thalamus has a moderate density of receptors. The density of receptors is lower in the hypothalamus. In the midbrain and pons, the density of receptors is high in the interpeduncular nucleus, locus coeruleus, and moderate in the periaqueductal gray region. The pons and medulla have a high density of receptors in the floor of the fourth ventricle, including components of the vagal system, spinal trigeminal nucleus, and the nucleus raphe magnus. In the spinal cord, the greatest concentration of receptors is in laminae I and II of the substantia gelatinosa. This extremely wide distribution of opiate receptor sites in the nervous system suggests that the opiates act by influencing many areas concerned with processing nociceptive stimuli, including the limbic system, thalamus, locus coeruleus, periaqueductal gray matter, nucleus raphe magnus, trigeminal and vagal nuclei, and the substantia gelatinosa.

Intrathecal administration of opiates has recently been reported to be an effective method of producing analgesia in animals and man. Yaksh and Rudy, using chronic spinal subarachnoid catheters in rats, showed that intrathecal morphine produced a dose-dependent elevation in the nociceptive threshold. Wang, et al., injected 0.5 to 1.0 mg of morphine into the lumbar subarachnoid space of eight patients with pain due to cancer. Pain relief occurred within 15 to 45 minutes of the injection, lasted 12 to 24 hours, and was not associated with sedation, neurological change, or respiratory depression. Tung, et al., obtained 30 hours of pain relief with 1 mg of lumbar intrathecal morphine in a patient with inoperable carcinoma of the pancreas. Subarachnoid injection, as near as possible to the affected spinal segments, of 10 to 30 mg pethidine (Demerol) or of 1 to 3 mg morphine, was made by Cousins, et al., in five patients with cancer. Complete relief of pain was obtained for up to 48 hours. In order to avoid repeated spinal puncture, they placed epidural spinal catheters and injected 30 mg of pethidine in 6 ml of saline. The mean duration of analgesia produced was 8 hours, with a range of 4.5 to 18 hours. Blood levels of pethidine in these patients were less than would have been required to produce analgesia if the drug had been administered intravenously. The patients had no motor weakness and no change in sensory or sympathetic function. Increasing the epidural dose of pethidine to 100 mg did not increase the duration of the analgesia, but did
produce mild sedation for 10 to 15 minutes. Samii, et al., have used a large dose of intrathecal morphine, 20 mg in a hypertonic solution of 10% dextrose, after which the patient was put in a 40° head-up position. Analgesia appeared in 26 minutes, peaked at 1 hour, and disappeared in about 27 hours. A sensory level to painful stimuli was detectable and ranged from T-1 to T-6 in the 10 patients treated. There was no change in touch sensation, motor function, heart rate, blood pressure, or respiratory rate. Sedation was moderate or absent.

We were encouraged by these studies to investigate the effectiveness of intrathecal morphine for control of chronic pain in patients with cancer.

Clinical Material and Methods

Six patients with intractable pain due to cancer were selected for a trial of intrathecal morphine. They had obtained unsatisfactory relief of pain with oral or parenteral narcotics. In these patients, if one or several injections of morphine sulfate in the lumbar subarachnoid space gave satisfactory pain relief for an adequate period of time, it was proposed that an Ommaya reservoir be inserted with its catheter tip in the lumbar subarachnoid space or lateral ventricle. The reservoir would then be used for percutaneous administration of morphine sulfate. If this treatment seemed to be satisfactory in the hospital, then it was planned to continue treatment at home, training a responsible family member (generally a spouse or a parent) to give the injections of morphine. One of the members of our pain team had the responsibility of teaching the family members aseptic technique for the injections. The hair over the Ommaya reservoir was kept shaved. Betadyne skin preparation was used, and No. 25 needles were used for injection. The site of the injection through the Ommaya reservoir was moved slightly each day.

Patients were asked to grade the intensity of their pain on a scale of 0 to 10, with 10 representing their maximum level of pain. Vital signs were monitored every 15 minutes for several hours after receiving a morphine injection, after which vital signs were taken hourly. Several patients, but not all, received a placebo of intrathecal saline solution. Neurological examination was performed on each patient after the morphine injections at a time when the patient was aware of either a reduction in pain, or of side effects such as paresthesia or itching.

In patients who had a catheter placed in the lumbar subarachnoid space (Fig. 1), the reservoir was placed on the fascia in a lean patient, and subcutaneously in obese patients. The catheter was placed in the subarachnoid space through an L-3 hemilaminectomy. A thin stainless steel disc was sewn against the flat bottom of the reservoir to act as a barrier to the injecting needle and to aid in placing the needle tip inside the reservoir. A technique we have previously described was used for the placement of a ventricular reservoir catheter system.

The chemical purity of the morphine solutions to be injected has been a source of concern to us. Approximately 15 patients have been reported in the literature to have had lumbar subarachnoid injections of morphine. In most, if not all, of those patients, the morphine solutions injected contained preservatives. The morphine source we initially used was Wyeth's 1-cc Tubex sterile solution, which contains 10 mg of morphine sulfate plus preservatives and buffers. The patients' calculated dose of morphine was taken from the 1-cc Tubex stock solution, mixed with 5 cc of preservative-free physiological saline, and kept in 5-cc disposable plastic syringes. The initial intrathecal dose of morphine sulfate used was in 5 ml of solution, which contained 0.5 mg of phenol and 0.1 mg of formaldehyde. Because of the inadequate amount of preservatives in these morphine preparations, the patients' syringes of sterile morphine were freshly prepared once a week. In order to further insure that the solution was free of bacteria, an in-line Millex-OR 0.22-μ filter unit* was inserted between the patient's morphine-containing syringe and needle.

Our pharmacy now provides us with sterile, preservative-free morphine sulfate solutions. The solution is prepared by dissolving a 10-mg morphine sulfate tablet in preservative-free normal saline.† The solution is filtered through a 0.45-μ filter into a Hollister-Stier pyrogen-free 10-ml vial which is auto-

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* In-line Millex-OR 0.22-μ filter unit manufactured by Millipore Corp., Bedford, Massachusetts.
† Morphine sulfate tablets made by Eli Lilly and Co., Indianapolis, Indiana. Knoll Pharmaceutical Co., Whippany, New Jersey, also supplies ampules of preservative-free morphine.
Intrathecal and intraventricular morphine claved at 256°F at 15 lb/sq in. for 25 minutes. These vials are prepared once a week and are kept in the refrigerator.

Results

Diagnostic Lumbar Intrathecal Morphine

In five patients, morphine sulfate administered via lumbar puncture was evaluated prior to Ommaya reservoir placement. This was not done in Case 6, a child who already had an Ommaya reservoir in place at the time we were asked to see him for pain alleviation.

Lumbar intrathecal morphine gave pain relief within 30 to 60 minutes of the injection in all cases. The pain level went from a grade of 10 to 0 in most cases, and to a level of 1 or 2 in others. The patients did not require analgesics and were able to be more active. An injection of 0.5 mg of morphine sulfate gave pain relief for 12 to 14 hours, and 1.0 mg morphine sulfate relieved the patients' pain for 10 to 25 hours. Increasing the dose to 2 mg did not improve the quality of pain relief or lengthen the period of relief. There was no significant change in vital signs as the result of lumbar intrathecal morphine injections. There was no change in the state of consciousness, and no alteration of the neurological examination. Two patients were given control injections of saline, which did not relieve their pain.

The only side effects were itching and perioral paresthesias. Generalized itching, which occurred 20 to 25 minutes after the injection, developed in two patients, but there was no skin rash. The itching was controlled with 50 mg of Benadryl (diphenhydramine) intramuscularly or orally at the time the morphine was given. One patient who continued to receive lumbar intrathecal morphine daily for many months stopped having itching associated with the morphine injections after the first 2 weeks. One patient had transient facial tingling for a few minutes, beginning 30 to 60 minutes after the injection.

Lumbar Intrathecal and Intraventricular Morphine per Ommaya Reservoir

An Ommaya reservoir was inserted in six patients to facilitate morphine injections for pain relief. The reservoir was placed in the lumbar region for intrathecal injection in two patients and in the right frontal region for intraventricular injection in four patients. The tumor diagnosis, the morphine dose, the duration of pain relief, and duration of morphine treatment in these patients are recorded in Fig. 2. The side effects for lumbar intrathecal morphine were as mentioned above. Intraventricular morphine caused transient nausea and vomiting within 10 to 60 minutes of the injection, treated with Compazine (prochlorperazine) or Phenergan (promethazine) in three patients; transient facial tingling began 10 minutes after the injection and lasted a few seconds to 1 to 2 hours in two patients.

The first patient, with carcinoma of the rectum, had recurrence of tumor in the pelvis causing pain in the rectum, sacrum, and vagina. Daily injections of 1 mg of morphine into her lumbar Ommaya reservoir gave her pain relief for 14 hours, allowing her to return to useful activities. Oxycodone (Percodan) would relieve her pain for the remainder of the day. After 3 months, she developed tolerance, requiring 2 mg of morphine every 8 hours in her reservoir for pain relief. Prior to her death, her pain was being controlled with 4 mg of morphine injected into her Ommaya reservoir every 8 hours, and intramuscular pethidine every 8 to 16 hours.

The patient with thyroid carcinoma had pain in her back, hips, and extremities. One mg of lumbar intrathecal morphine would relieve her pain for 10 hours. Several days after the insertion of a lumbar Ommaya reservoir, the T-12 vertebral body collapsed and she became paraplegic. Lumbar intrathecal injections of morphine did not relieve her pain since the morphine could not reach the spinal cord.

Sarcoma of the vulva in the third patient had metastasized to the mediastinum, chest wall, and stomach, causing pain in the chest and abdomen. Morphine, 2½ mg, injected in the right lateral ventricle via an Ommaya reservoir relieved her pain for 12 hours and made it possible for her to be more active at home. Her morphine requirements remained the same for 2 months. Tolerance developed so that morphine requirements increased in the last 2 months of her life. During that time, she required 4 mg of morphine in her Ommaya reservoir, giving her pain relief for 24 hours.

The patient with osteogenic sarcoma of the sacrum had pain located in the sacrum, hips, and legs. Doses of pethidine (100 mg), alternating with 4 mg of hydromorphone (Dilaudid), intravenously every 2 hours gave her inadequate pain relief and left her drowsy. She was also receiving 50 mg of amitriptyline (Elavil) daily for depression. In this patient, 4 mg of intraventricular morphine was required to relieve her pain, but the duration of relief varied from 12 to 24 hours. She also developed tolerance, so that after 2 months 5 mg of morphine, and after 3 months 7 mg of morphine was required to relieve her pain. Personal follow-up review could be maintained for only 3 months. She was reported to have subsequently undergone a bilateral cordotomy.

The last two patients whom we have treated with intraventricular morphine were in the terminal stage of their disease and lived only a short period of time. Intraventricular morphine resulted in excellent pain relief in both patients. The adult patient had recurrent carcinoma of the cervix, bilateral obstructive uropathy, and pain in her back and both lower extremities. Daily injections of 4 mg of morphine in her Ommaya reservoir gave her 24 hours of pain relief. This treat-
ment was continued for 23 days, but was not required in the last 2 days of her life because of terminal uremia.

The 5-year-old boy had Burkitt's lymphoma with tumor in bone and meninges and a large tumor mass in his abdomen. His greatest pain was in his abdomen. One-half mg of intraventricular morphine relieved his pain completely for 18 hours and partially for another 3 hours.

Discussion

Morphine applied intrathecally in the lumbar region or in the lateral ventricle will relieve pain within an hour of the injection. The minimum effective initial dose in adults was 1 mg of morphine in the lumbar region, and 2.5 to 4.0 mg intraventricularly. Pain relief ranged from 80% to 100%.

None of the side effects of intrathecal or intraventricular morphine was annoying enough for the patients to want to return to oral or parenteral narcotics. We do not know at this time if the side effects were due to morphine or the small quantities of preservatives present. None of our patients developed infections of their Ommaya reservoir injection sites or meningitis, even though three patients received daily injections for 3 to 7 months.

There was no evidence of damage to nerve roots or the central nervous system as a consequence of morphine treatment. Drowsiness, lethargy, and sedation did not develop with intrathecal or intraventricular morphine.

There are several reports in the literature of delayed respiratory depression occurring in patients who received intrathecal morphine, usually in connection with general anesthesia or spinal anesthetic agents. These patients had received 1 to 15 mg of morphine, injected intrathecally. Respiratory depression was not noticed until 4 to 11 hours after injection, and was reversed by naloxone. We have not observed respiratory depression in the patients we have treated.

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**Fig. 2. Summary of requirements and results of intrathecal and intraventricular morphine administration in six patients.**

Carcinoma-Rectum  Carcinoma-Thyroid  Sarcoma-Vulva  Sarcoma-Sacrum  Carcinoma-Cervix  Burkitts Lymphoma

<table>
<thead>
<tr>
<th>MONTHS</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
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<td>PATIENTS</td>
<td>1-Female, Age 40</td>
<td>2-Female, Age 36</td>
<td>3-Female, Age 27</td>
<td>4-Female, Age 24</td>
<td>5-Female, Age 49</td>
<td>6-Male, Age 5</td>
<td></td>
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HOURS OF PAIN RELIEF

Circled numbers = mg. Morphine sulfate
P = Paraplegia due to cord compression
L = Lost contact and control of patient
D = Died
C = Cordotomy
Intrathecal and intraventricular morphine

with 1 to 7 mg of intrathecal or intraventricular morphine. Because of the possibility of this serious side effect, each patient who is beginning treatment with intrathecal or intraventricular morphine, or who is having an increased dose administered, should be treated and monitored in an intensive care area.

Our experience, although limited, is that intrathecal and intraventricular morphine can be used effectively for many months without harm. It can be used in patients whose disease progression and pain distribution is such that traditional neurosurgical pain-relieving procedures are not indicated. Contraindications to the use of Ommaya reservoir placement for chronic drug administration are: infection and an absence of a reliable adult family member or nurse in the community to give the morphine injections when the patient is at home.

Additional experience is needed to determine which patients are likely to benefit from intrathecal or intraventricular opiates and which site of delivery of the narcotic is preferable. Experience with various narcotics is needed to determine the optimum dose and drug. Implantable reservoirs which perfuse a measured dose of opiates daily, and which can be refilled percutaneously every few weeks or months will likely be used for relief of intractable pain.

References

10. Snyder S: The opiates, opioid peptides (endorphins), and the opiate receptor. Texas Med 75:41-45, 1979

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