Continuous intrathecal hydromorphone and clonidine for intractable cancer pain

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Continuous intrathecal and epidural morphine administration has been shown to relieve pain in patients with metastatic cancer. Until now, no alternative nonpeptide narcotic agents have been substituted for morphine in the continuous intrathecal or epidural delivery of drugs via implanted infusion devices. Such a substitute would be valuable for treatment of patients with significant sensitivity or allergy to morphine. In addition, some authorities argue that cancer patients with apparent tachyphylaxis to one narcotic can be treated with significantly reduced dosages of a second narcotic agonist when agonist dosages are expressed in narcotic potency equivalents. The mechanism for this effect by a second agent is unknown, although different profiles of receptor affinity for one or more subgroups (mu, delta, or kappa) of opiate receptors may be responsible. Extrapolating to spinal opiate receptors, an alternative spinal narcotic agonist might also be effective at comparatively lower dosages when advanced tolerance to intraspinal morphine develops.

In this report we document the use of an intrathecal infusion of the mu-agonist hydromorphone (Dilaudid) in successfully treating the cancer pain of a patient with a history of severe sensitivity to morphine. When advanced tolerance to hydromorphone developed, the alpha2-agonist clonidine was concomitantly infused intrathecally to again yield analgesia. This stepwise approach represented a successful alternative to nerve destruction in the management of the cancer pain in this patient, who steadfastly refused neurolytic or nerve section techniques for pain control.

Case Report

This 49-year-old woman was diagnosed in 1980 as having stage 1 uterine cervical carcinoma. She had previously given birth to seven children. Radical Wertheim hysterectomy and bilateral pelvic lymphadenectomy revealed no nodal metastasis; however, right lower-quadrant pain appeared in 1982. Reexploration in September, 1983, revealed recurrent tumor involving the right pelvic sidewall, and right kidney obstruction was noted on a bone scan in October.

Treatment. Radiation treatment was given, with 4400 rads to the pelvic and femoral nerve area, along with administration of bleomycin (225 U) and cisplatin (170 mg). In January, 1984, the patient suffered right-leg pain, which required 100 mg/day of methadone. A three-field radiation boost was given to the pelvic sidewall (6000 rads in total) along with further bleomycin (102 U) and cisplatin (170 mg). Computerized tomog-
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CT scans showed a large right pelvic mass displacing the soft tissue and right side of the ureter; substantial shrinkage occurred following irradiation. Pain decreased and methadone intake was reduced to 20 to 30 mg/day.

The patient returned to work, but 2 months later she suffered a right femoral vein thrombosis for which coumarin anticoagulation was initiated. Her oral narcotic requirement gradually increased to 60 mg/day of methadone alternated with hydromorphone (2 mg) doses until she was referred to our institution in April, 1984. Her primary complaint was a deep, aching, nearly constant pain which radiated from the low back to the groin, anterior aspect of the thigh, and knee. Hyperpathia was present over the anterior portion of the thigh. Moving and weight-bearing exacerbated the pain. Overall, motor strength was normal, although strength in the right thigh could not be assessed due to pain. Thigh and knee reflexes were asymmetrical; deep tendon reflexes and ankle jerks were +1 on the right versus +3 on the left. She could still walk with a cane but needed occasional wheelchair support.

Because of causalgic pain components, local anesthetic lumbar sympathetic blocks were tried without effect. The patient refused both cordotomy and intrathecal neurolysis, but subsequently agreed to enter a controlled study of continuous intrathecal narcotic versus conventional oral narcotic manipulation. As a component of this study, a formal psychiatric interview and Carroll Depression Scale test were performed. Neither suggested that depression contributed significantly to her report of pain. The patient was randomly assigned to the conventional narcotic control group, and her methadone dosage was progressively increased to 120 mg/day with intermittent hydromorphone up to 12 mg/day. Oral amphetamine, 5 mg, was added to counteract sedation. One month later she was readmitted for pain control on this regimen. Her right-leg weakness had progressed, and she now required a walker to ambulate. Moderate constipation was present along with difficulty in initiating urination.

**Pump Implantation.** The patient again refused chemical or surgical neurolysis; a crossover to the continuous intrathecal narcotic group was permitted by our study protocol. However, she related a history of morphine intolerance characterized by severe nausea, vomiting, and migrainous headaches. She adamantly refused to receive morphine by any route, although intrathecal hydromorphone was an acceptable alternative.

Thus, an Infusaid reservoir* was implanted in series with an L4–5 intrathecal silicone catheter. Initial analgesia was obtained with a 1.5-mg/day intrathecal infusion of hydromorphone. Coumarin administration was halted 2 days before and restarted 2 days after implication of the reservoir. This initial postoperative period was complicated by spinal headache which resolved after an epidural blood patch. Oral clonidine (0.5 mg/day) was initiated immediately after pump implantation to block narcotic withdrawal symptoms, and methadone was decreased from 120 to 24 mg/day. The patient was discharged on the 6th postoperative day, receiving 2.4 mg/day of intrathecal hydromorphone.

**Second Admission.** The patient was readmitted 2 months postimplantation for evaluation of rectal and nose bleeding. Coumarin was discontinued. After transfusion of blood (2 units) and fresh frozen plasma (1 unit) she was discharged. Although she could still ambulate with a walker, further right-leg weakness and some ipsilateral breakthrough pain were manifest with weight-bearing. Figure 1 shows the patient's serial Visual Pain Analogue Scale reports plotted as 5-day mean pain intensity values, daily oral narcotic intake in morphine equivalents, and dosages of intrathecal hydromorphone required. It can be seen that her pain initially stabilized at 10 mg/day of intrathecal hydromorphone. Because of hydronephrosis, a palliative chemotherapy trial (1600 mg cyclophosphamide and 2 mg vincristine) was given to shrink the tumor.

After 2 months of continuous intrathecal infusion,
the pain had again worsened, despite daily dosages of 15 mg intrathecal and 24 mg oral hydromorphone. The pelvic mass was now shown by CT scan to measure 12 × 14 cm. Given the pump’s fixed flow rate (2.3 ml/day), further intrathecal hydromorphone dosage increases were limited. The patient was switched to a second intrathecal drug protocol. An intrathecal 0.3-mg injection of clonidine yielded 7 hours of almost complete pain relief, so intrathecal clonidine infusion was initiated at 0.4 mg/day. Initially she experienced hypotension to 76 mm Hg systolic pressure, which was successfully countered with oral ephedrine and intramuscular vasopressin. She was discharged on a regimen of 5 mg/day intrathecal hydromorphone and 0.75 mg/day intrathecal clonidine. Figure 1 also reveals the timing of intrathecal clonidine initiation and serial hydromorphone dosage adjustments to control pain. The patient remained at home until her death from vaginal hemorrhage in mid-October, 1984. The peak hydromorphone and clonidine doses during this last month were 15 and 1.5 mg/day, respectively.

Pathological Examination. Postmortem examination revealed pelvic tumor involving the bladder, rectum, and small bowel mesentery. There was also pelvic radiation fibrosis and right hydronephrosis. Widespread tumor invasion of the lumbosacral plexus was consistent with the pain reported. Histological examination of the spinal cord revealed no apparent demyelination or gliosis of the posterior columns (Fig. 2). The neurons of the anterior horns were intact; no vacuolation or central chromatolysis was observed. High-pressure liquid chromatography with electrochemical detection was used to analyze cerebrospinal fluid (CSF) drawn from the sideport of the implanted pump during steady-state infusion of hydromorphone (15 mg/day) immediately prior to intrathecal clonidine initiation. (This technique, with a detection limit for morphine and hydromorphone of 10 ng/ml, has previously been reported.)

The third of three 1.5-ml CSF aliquots was analyzed; analysis of serial CSF aliquots indicated that hydromorphone concentrations asymptotically approximated but did not exceed the concentration obtained by concomitant lumbar puncture (DW Coombs, RW Colburn, unpublished data, 1984). Retrospective review revealed that this patient had received at least 780 mg intrathecal hydromorphone and 39 mg intrathecal clonidine, with a potential peak steady-state CSF hydromorphone concentration of 24.5 μg/ml without apparent neurotoxicity.

Discussion

Hydromorphone has been shown to provide significant analgesia when given epidurally to postoperative patients. Administration of 1.5 mg epidural hydromorphone provides postoperative analgesia for approximately 6 to 8 hours, a period intermediate between that achieved with epidural meperidine and morphine. To our knowledge, this is the first patient treated with a continuous intrathecal infusion of hydromorphone. Therefore, several important facets of this case deserve mention. First, intrathecal hydromorphone provided adequate complication-free analgesia for 2 months, until tolerance and/or progression of disease led to increasing intrathecal dosage escalation and finally to introduction of an adjunctive intrathecal agent (clonidine hydrochloride). In this regard, hydromorphone behaved similarly to intrathecal morphine in our preliminary trials. We have previously observed that terminal cancer pain is initially controlled with epidural or intrathecal morphine infusion; however, after 2 to 3 months there is often a progressive attenuation of pain control. Continuous intrathecal hydromorphone resulted in no apparent neurotoxicity. Nausea, vomiting, and itching, commonly seen following bolus administration of spinal narcotics, did not occur. Urinary retention, also a frequent side effect of intraspinal narcotic injection given for postoperative pain, was more difficult to assess in our patient due to confounding problems: namely, hydronephrosis, administration of irradiation and chemotherapy, and pelvic neuronal injury from the tumor. Notably, she had recurrent urinary tract infections and bacteremia, which might have been aggravated or precipitated by hydromorphone-induced urinary retention.

The agent hydromorphone was selected because of this patient’s history of violent nausea, vomiting, and migrainous headache following previous administration of parenteral morphine. In contrast to morphine, she had taken oral hydromorphone uneventfully. She refused a trial of intrathecal morphine despite the fact that hydromorphone and morphine are structurally similar. Hydromorphone may have other advantages when compared with intrathecal morphine. Hydromorphone is generally considered to be more lipid-soluble, although this has been challenged recently. Higher narcotic lipid-solubility theoretically leads to larger ros-
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trocaudal CSF concentration gradients and thus a greater proclivity to regionalize to the lower spinal cord (the spinal catheter was introduced at L4–5)." The property may reduce the risk of respiratory depression, at least in the setting of acute bolus administration. Such considerations may have little practical importance, since chronic pain patients are reported to experience less risk of respiratory depression during acute or chronic intraspinal narcotic therapy. Hydroxymorphone also has greater potency than morphine and is available in a concentrated preservative-free preparation. Houde stated that 1.5 mg intramuscular hydromorphone is equivalent to about 7.5 to 10 mg intramuscularly. According to this comparison ratio, intrathecal infusion of 3 ml/day of a 10-mg/ml hydromorphone solution is equivalent to more than 100 mg intrathecal morphine per day. Additionally, hydromorphone is stable at 37°C and compatible with clonidine during chronic intrathecal infusion via an implanted infusion pump (DW Coombs, et al., unpublished data, 1984).

Tolerance continues to be an obstacle with chronic intrathecal administration of narcotics. In the final days of a patient’s illness, drastic escalation of intrathecal narcotic may be acceptable in order to control pain. However, the neurological consequences of protracted intrathecal infusion of concentrated narcotic solutions have yet to be rigorously and scientifically documented. Anecdotally, myoclonic jerking was observed in two patients during infusion of high concentrations of intrathecal morphine. Therefore, alternative pharmacological approaches need to be developed for extended pain control, if nerve section procedures are to be avoided.

Studies by both Tamsen and Gordh and our laboratory indicate that intrathecal clonidine produces minimal neurotoxicity. The spinal cord lesions observed during postmortem examination in our series of chronic cancer pain patients were diagnosed as parenchymal necrosis secondary to compression by invading tumor, chemical neurolysis-induced neuronal vacuolation, and posterior column degeneration. In contrast, the spinal cord of this patient had intact white and gray matter. We have also recently documented successful, although temporary, use of intrathecal clonidine in a patient with substantial tolerance to intrathecal morphine in whom a protracted course likely contributed to ultimate failure of pain control. However, the patient described here derived pain control from the intrathecal hydromorphone-clonidine combination until her death. As Foley has suggested, there may be other useful opiate receptor agonists with greater efficacy at reduced intrathecal dosages, as judged by narcotic potency equivalents. Unfortunately, this could not be tested in this setting.

In conclusion, intrathecal hydromorphone may produce analgesia in patients with severe cancer pain when infused continuously via an implanted pump. As with intrathecal morphine, increased dosage requirements of hydromorphone in some cases will necessitate alternative approaches to control terminal pain.

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References


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