Patient-Controlled Analgesia for Chronic Cancer Pain in the Ambulatory Setting: A Report of 117 Patients

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Patient-controlled analgesia (PCA) represents a drug-delivery system in which patients self-administer predetermined doses of opiate analgesics. We have taken advantage of recent advances in pump technology and developed a system in which patients with severe pain received a continuous narcotic infusion, along with the capability of PCA bolus for breakthrough pain. All patients were experiencing chronic pain related to cancer and were unable to obtain adequate pain control with either intermittent parenteral, oral, or rectal narcotics. Sixty-nine percent of patients were treated in the home setting, and the majority received morphine sulfate subcutaneously (SQ). Admixture stability studies using high-pressure liquid chromatography (HPLC) showed that dexamethasone, metoclopramide, and haloperidol could be added to the morphine solutions and remain stable for 1 week at room temperature. Of 117 patients entered, 95% received excellent pain control, and side effects were rare, consisting of subcutaneous needle site infection and respiratory depression. Progressive pain due to either advancing disease or development of drug tolerance could be controlled by increasing opiate infusion rates. We conclude that (1) continuous infusion opiate with PCA bolus capability can be initiated and administered safely in the home setting; (2) patients with pain related to malignancy can be managed well with this system; and (3) pain control programs can be designed, implemented, and evaluated in the private practice setting.

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THE OPTIMUM management of chronic pain in the individual with terminal cancer is a subject of great importance to both patient and physician.[1] The cancer site and the stage of disease are important factors in determining which patients will encounter problems with pain control.[2,3] At least two thirds of cancer patients in the final stages of their disease will report significant pain, and it has been estimated that 25% of all cancer patients throughout the world will die without relief from severe pain.[2,4] Often accompanying this pain are problems with depression, anxiety, hostility, and decreased level of activity.[5] Adequate pain control can clearly result in an improved overall quality of life.[6]

Narcotic analgesics form the cornerstone in the management of moderate to severe cancer pain.[1] Alternatives to the oral route of administration may become necessary in certain settings, including protracted nausea and vomiting, bowel obstruction, malabsorption, mucositis, and inadequate pain relief in spite of large oral doses. Alternate methods of administration have included sublingual/buccal,[7] intravenous (IV) infusion,[8] subcutaneous (SQ) infusion,[9] rectal,[10] epidural/intrathecal,[11,12] intraventricular,[13] and transdermal.[14] Clinical experience has shown that while most cancer patients initially can be managed with oral medications, alternate routes of administration are frequently necessary as their disease progresses.[15]

The principles of patient-controlled analgesia (PCA) have been applied effectively in the management of postoperative[16] and obstetrical[17] pain. In this setting, patients self-administer predetermined doses of opiate analgesics. We have used this concept in the management of chronic cancer pain using either the IV or SQ routes, and report here our experience with 117 consecutive patients who were treated in a private-practice setting.

MATERIALS AND METHODS

Patient Population

All patients in the greater Monterey, CA area placed on PCA between July 1, 1985, and April 30, 1988, were included in this study. This was possible because narcotic infusion pumps in our area are available through only one pharmacy that specializes in outpatient and home care. Patients were cared for in the inpatient and outpatient settings by a small group of oncologists and internists. All patients had to be experiencing chronic pain related to cancer with the inability to obtain adequate pain control with either oral, rectal, or intermittently injected narcotics. Also, the patients and their

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families had to demonstrate the ability to understand the principles involved in PCA and pump management. All patients rated their pain just before PCA initiation on a scale of 0 to 5, with 0 representing no pain and 5 representing excruciating pain. Reassessment took place upon attainment of a steady opiate infusion rate.

Method of Delivery

Patients were begun on PCA in both the inpatient and outpatient settings. As our experience grew, we developed and refined policies and procedures for initiating PCA in the patient's home with a home-care nurse in attendance. Initial infusion rates, bolus doses, and minimum bolus frequency were calculated by the physician and pharmacist, and a specific protocol for dose escalation was followed.

All patients in this study used the CADD-PCA pump (Pharmacia-Deltec, St Paul, MN) and received a basal infusion of opiate supplemented by additional boluses that were self-administered. Initiation doses were determined by using an equalanalgesic conversion chart (Table 1) to convert the prior 24 hours of opiate usage into parenteral equivalent with no dose adjustments made for cross tolerance.[1] Dividing this value by 24 yielded an appropriate initial hourly basal-infusion rate. The bolus dose was approximately 25% of the hourly infusion dose. The initial physician orders had to include not only the starting hourly and bolus doses, but also a rate of increase in the basal rate (generally 10% to 20% every 60 minutes) and the minimal time interval between bolus doses.

The initiation procedure began with a nursing assessment of baseline blood pressure, heart and respiratory rate, level of consciousness, and pain level. A minority of patients opted to have naloxone at the bedside and were instructed in its use. The administration of narcotic was initiated with a bolus dose followed immediately thereafter by the basal infusion. If the pain level was unsatisfactory after 60 minutes and the patient was clinically stable, an additional bolus was administered, and the basal rate increased by the prescribed amount. The patient was reassessed on an hourly basis until adequate analgesia was achieved. If, after 4 hours of monitoring and dosage adjustments the pain level remained unacceptable, the physician was notified, and further decisions were made on the basis of the overall clinical situation. Pain level was reassessed when an acceptable steady infusion rate had been achieved.

Policies for PCA therapy required that home initiations be started early in the day, with the prescribing physician available by telephone for dosage determination and consultation. The initiation nursing visit was a minimum of 3 to 4 hours in length; occasionally a second visit for assessment was required in the evening. Policy also required that a responsible individual such as a family member or friend be present during PCA initiation in the event of any problems.

Table 1. Equianalgesic Conversion

Narcotic	Parenteral Dose (mg)	Oral/Rectal Dose (mg)
Morphine	10	30
Hydromorphone	1.5	7.5
Oxycodone	—	15
Oxymorphone	—	10
Meperidine	75	300
Methadone	10	20
Levorphanol	2	4
Codeine	130	200

Upon attainment of a steady infusion rate and acceptable pain relief, the number of bolus doses required per 24 hours became the guideline for determining subsequent dose adjustments. With rare exceptions, the minimum time interval between bolus doses was 60 to 120 minutes in stable patients. For those patients on SQ infusions, the needle site was changed every 48 hours or as necessary.

Once patients had achieved a steady state, they received daily telephone contact with scheduled nursing visits every other day for assessment of pain and clinical status, SQ needle site change, medication reservoir replacement, and pump check. Medical, nursing, and pharmacy services were available 24 hours per day for any pump- or therapy-related problems.

Chemical Additives

To examine the feasibility of adding additional medications to the narcotic infusion, stability studies were performed. Dexamethasone, metoclopramide, and haloperidol were added individually to morphine solutions with the potential benefit of controlling inflammation at the SQ site, nausea, and combative behavior, respectively. These admixtures were examined for chemical degradation at Smith-Kline Laboratories (Burlingame, CA), using high-performance liquid chromatography (HPLC) after 7 days at room temperature. The concentrations tested were as follows: morphine sulfate (15 mg/cm^3) plus dexamethasone (.02 mg/cm^3); morphine sulfate (15 mg/cm^3) plus metoclopramide (1.0 mg/cm^3); and morphine sulfate (15 mg/cm^3) plus haloperidol (.2 mg/cm^3).

RESULTS

Patient Characteristics

One hundred seventeen consecutive patients placed on the PCA pump were included in this study. Table 2 summarizes the important characteristics of these patients. There was a wide age range with a predominance of males. Most patients were treated in the home setting, and morphine was the most commonly used analgesic. The IV route was used infrequently, and the mean duration of treatment was approximately 3 weeks. The sources of pain in these patients are listed in Table 3. The most common indication for initiation of PCA was uncontrolled bone pain. The analgesic history immediately prior to initiation of PCA is included in Table 4. The majority of patients were receiving some form of parenteral narcotics at the time of entry to this study.

Patient Outcome

The pain rating scale used in assessing the degree of pain in our patients is included in Fig 1.

Table 2. Patient Characteristics

No. of patients	117
Age	
Range	28 to 90 yr
Mean	61.2 yr
Sex	
Male	72/117 (62%)
Female	45/117 (38%)
Treatment setting	
Home	81/117 (69%)
Hospice-SNF	36/117 (31%)
Narcotic prescribed	
Morphine sulfate	109/117 (93%)
Hydromorphone	8/117 (7%)
Route of administration	
Intravenous	15/117 (13%)
Subcutaneous	102/117 (87%)
Duration of therapy	
Range	1 to 295 days
Mean	23 days

Ninety-five percent (111) of our patients experienced pain relief after initiation of PCA. Their level of pain decreased from a mean of 4 to a mean of 1 (Fig 2). All responding patients achieved pain control within 12 hours of initiation of the PCA protocol. With rare exceptions, progressive pain with advancing disease was well controlled by increasing opiate infusion rates. Of the 111 patients who did well with the pump, all but two remained on PCA until their death. There was a wide range in the amount of narcotic required to achieve adequate analgesia (Table 5), with the patients on IV morphine receiving a larger dose than those on SQ infusion. Of the 15 patients on the IV infusion, six were initially begun on SQ and subsequently switched to IV because of high narcotic dose requirements or irritation/pain at the SQ injection site. Additional nonquantified, subjective outcomes noted by both patients and health professionals included a frequent decrease in anxiety and a lessening of dependence on caregivers. Complications developed in two patients (Table 6). One patient developed a SQ site infection that was eradicated by a course of IV antibiotics. A

Table 3. Pain Syndromes

Syndrome	No. of Patients (%)
Bone pain	54/117 (47)
Abdominal-pelvic pain	25/117 (22)
Generalized pain	24/117 (24)
Other (eg, head and neck pain nerve compression)	14/117 (11)

Table 4. Opiate Analgesic History

Analgesic History	No. of Patients (%)
Oral opiates only	50/117 (43)
Parenteral opiates only	28/117 (24)
Oral and parenteral narcotics only	31/117 (26)
Rectal narcotics only	8/117 (7)

second patient with significant impairment of his upper airway and intractable head and neck pain secondary to recurrent oral cancer experienced a respiratory arrest within 24 hours of PCA initiation and could not be resuscitated. While we cannot be certain of the role morphine played in this setting, we have chosen to include this as a treatment-related complication. During the 34 months of this study, pump-malfunction alarms were activated on three occasions, indicating pump microprocessor failure, which required a new pump. In all circumstances, the pumps were changed within one hour, and there were no adverse clinical consequences. Six of 117 patients (5%) did not achieve acceptable levels of pain control with the PCA system. Reasons for failure included (1) SQ needle discomfort secondary to minimal SQ tissue with unwillingness to proceed to IV infusion (three patients); (2) intolerance of morphine-related side-effects with return to the previous analgesic (two patients); and (3) psychological inability to accept dependence upon a pump for pain control with return to intermittent injections (one patient). None of the patients who opted to have naloxone at the bedside received this drug.

Additive Usage and Stability

Stability testing of the morphine/dexamethasone, morphine/metoclopramide, and morphine/haloperidol admixtures using HPLC revealed no significant chemical degradation after 7 days at room temperature. Dexamethasone was administered to 23 of 117 patients (20%), using a concentration range of .02 to .08 mg/cm^3 (average, 0.04 mg/cm^3). Eight of 117 (7%) patients received metoclopramide at a range of 10 to 40 mg/day (average, 16 mg/day at 0.7 mg/cm^3). Haloperidol was used in 10 of 117 patients (9%) at a range of 2 to 10 mg/day (average, 3.7 mg/day at 0.15 mg/cm^3). There was a subjective impression that these additives were helpful in controlling SQ site irritation, nausea, and agitation, respectively, but this study was not designed to enable us to quantitatively assess efficacy.

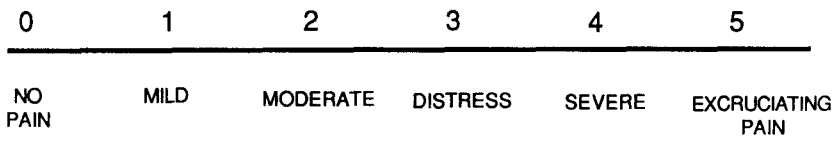

Fig 1. Pain rating scale.

DISCUSSION

The concept of PCA has been present in the medical literature for approximately 20 years. However, only recently have advances in pump technology and understanding of opiate pharmacokinetics allowed investigators to systematically examine the optimum use of this approach to pain control.[18-20] Using this method, patients are able to self-administer predetermined doses of analgesics, given either IV or SQ. A wide variety of programmable pumps are available. Some provide continuous infusion or "on demand" bolus narcotic doses only, whereas others have the capability of both modes of delivery.[20]

Experience with PCA in the postoperative and obstetrical settings has demonstrated its safety and effectiveness. When compared to standard postoperative intramuscular (IM) injections, patients on PCA experience less sedation and use less narcotics with equivalent analgesia. In addition, these patients express a greater satisfaction with their method of pain control.[21] The PCA system accommodates the wide range of narcotic requirements found among individual patients.[22]

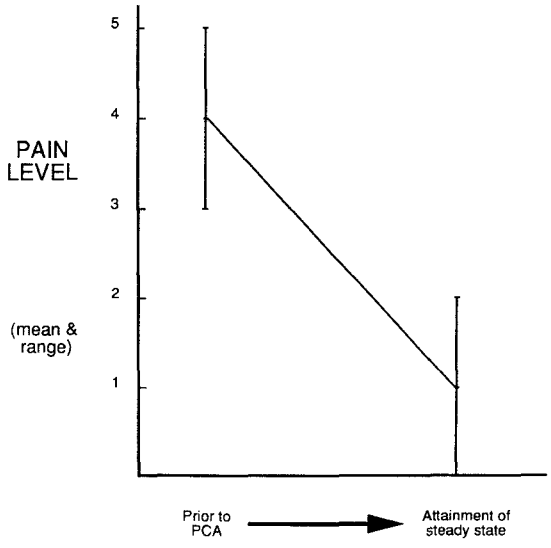

Fig 2. Patient rating of pain level.

The time lag between recognition of analgesic need and attainment of pain relief is reduced, and there is significantly less dependence on nursing or family help in pain control.[21]

Continuous infusion of opiates has been used in chronic pain patients. This has been particularly helpful when (1) patients require frequent IM or IV injections; (2) patients experience unacceptable side effects from the peak narcotic levels obtained with injections; and (3) rapid titration of drug dose is necessary.[23] Both the IV and SQ routes have been investigated, and they avoid the problems associated with wide swings in serum analgesic concentrations seen with traditional intermittent dosing methods.[24] In one study involving terminal cancer patients, acceptable pain relief with IV continuous infusion narcotics was obtained in 60% of patients.[25] SQ infusion, which avoids the problems with chronic venous access, has also been found to effectively control chronic cancer pain.[26] The major problem with analgesic pumps, which provide only continuous infusion without intermittent bolus capability, is that they provide no accommodation for the wide variation in analgesic requirements frequently encountered in cancer patients. Also, they do not deal with the problem of incident pain; that is, pain that is minimal at rest but immediately intensifies with movement.

The amount of data available on PCA in cancer patients is limited. Several previous studies have looked at the use of PCA for chronic cancer pain,[27-29] but these have used small numbers of patients followed for relatively brief periods of time. Also, in two of these studies,[27,28] only the bolus mode of PCA was used. A recent abstract reported a randomized study in bone marrow transplant patients, comparing PCA and continuous infusion morphine for mucositis pain.[30] The pain control achieved by the two methods was equivalent, but the PCA group used less morphine and reported less nausea.

We have taken advantage of recent advances in pump technology and offered our patients a

Table 5. Narcotic Dosages

	Basal Infusion (mg/hr)		Bolus Dose (mg)	
	Range	Mean	Range	Mean
Morphine SQ	1 to 33	6.5	0.5 to 15	4
Morphine IV	2 to 180	24	2.0 to 12	4
Hydromorphone SQ	0.3 to 21	3	0.5 to 1.5	1

system in which they receive a continuous opiate infusion along with the capability of PCA bolus for breakthrough pain, defined here as any temporary unacceptable increase in pain level that is experienced during a continuous narcotic infusion. Our study is notable in two respects. First, this represents the largest reported series of cancer patients using PCA for chronic pain. Second, while previous data has been generated from academic institutions, this study was conducted within the framework of a private-practice setting, incorporating a community-based, multidisciplinary approach.

We have demonstrated that continuous infusion morphine with PCA bolus capability can be safely used in the community, and that this system can be initiated in the home setting. Obviously, this is dependent upon the presence of well-trained and available medical, nursing, and pharmacy personnel with an ongoing commitment to close patient supervision. Excellent control of even severe pain can be achieved and maintained with patients retaining the option of remaining in the home setting for their care.

Our preference is to use the SQ rather than the IV route for narcotic infusion. Nursing management of the SQ route is easier, and problems associated with central venous catheters, such as infection or thrombosis, are avoided. The major factors affecting the decision to switch from the SQ to the IV route are the volume of morphine infused and SQ site irritation, which becomes an important consideration with more concentrated morphine solutions. This generally becomes prohibitive at levels greater than 40 to 50 mg morphine/hour given SQ (at 40 mg morphine/cm^3), and IV infusion then becomes necessary.

Our admixture stability studies show that, at the concentrations we used, selected additional drugs can be added to the morphine solution. A previous study has shown that antiemetics can be effectively added to SQ morphine infusions to control nausea and vomiting.[31] However, stability studies of the morphine/metoclopramide admixture were not performed in that report. Dexamethasone and haloperidol offer the additional potential benefits of controlling SQ injection site irritation and agitation, respectively. This method has the disadvantage of changing the additive infusion rate as the analgesic infusion rate is altered. Statements regarding efficacy will require randomized double-blind studies of symptom control.

Table 6. PCA Complications

Complication	No. of Patients (%)
SQ site infection	1/102 (0.9)
Respiratory depression	1/117 (0.8)

The financial implications of this study are substantial. Currently, many cancer patients with severe pain who require parenteral narcotics receive much of their care at inpatient facilities. The use of portable PCA pumps will allow many of these patients to be managed in the home setting. These pumps can be purchased by individual practitioners, hospitals, or pharmacies with a general price range of $2,500 to $3,500 per pump. Many of these patients are already being monitored by home-care nurses; therefore, additional costs incurred from nursing visits for PCA supervision will not be large. In addition, Medicare has recognized this method of drug delivery and will reimburse for pump rental, morphine administration, and disposables.

While conducting this study, we developed the strong impression that this system not only produced pain control, but also had a very favorable impact on numerous other aspects of the quality of our patients' lives. These benefits included a lessening of anxiety and depression, decreased sedation, increased mobility, and a greater sense of control over their own pain management. Tools are now available for quantitatively assessing quality of life in cancer patients, and we are now in the process of extending our investigations into this area.[32,33]

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