Subcutaneous narcotic infusions for cancer pain: treatment outcome and guidelines for use

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Objective: To provide guidelines for the institution and maintenance of a continuous subcutaneous narcotic infusion program for cancer patients with chronic pain through an analysis of the narcotic requirements and treatment outcomes of patients who underwent such therapy and a comparison of the costs of two commonly used infusion systems.

Design: Retrospective study.

Setting: Tertiary care facilities and patients' homes.

Patients: Of 481 patients seen in consultation for cancer pain between July 1987 and April 1990, 60 (12%) met the eligibility criteria (i.e., standard medical management had failed, and they had adequate supervision at home).

Intervention: Continuous subcutaneous infusion with hydromorphone hydrochloride or morphine started on an inpatient basis and continued at home whenever possible.

Outcome measures: Patient selectivity, narcotic dosing requirements, discharge rate, patient preference for analgesic regimen, side effects, complications and cost-effectiveness.

Results: The mean initial maintenance infusion dose after dose titration was almost three times higher than the dose required before infusion (hydromorphone or equivalent 6.2 v. 2.1 mg/h). Eighteen patients died, and the remaining 42 were discharged home for a mean of 94.4 (standard deviation 128.3) days (extremes 12 and 741 days). The mean maximum infusion rate was 24.1 mg/h (extremes 0.5 and 180 mg/h). All but one of the patients preferred the infusion system to their previous oral analgesic regimen. Despite major dose escalations nausea and vomiting were well controlled in all cases. Twelve patients (20%) experienced serious systemic toxic effects or complications; six became encephalopathic, which necessitated dose reduction, five had a subcutaneous infection necessitating antibiotic treatment, and one had respiratory depression. The programmable computerized infusion pump was found to be more cost-effective than the disposable infusion device after a break-even point of 8 months.

Conclusions: Continuous subcutaneous infusion of opioid drugs with the use of a portable programmable pump is safe and effective in selected patients who have failed to respond to standard medical treatment of their cancer pain. Dose titration may require rapid dose escalation, but this is usually well tolerated. For most communities embarking on such a program a programmable infusion system will be more cost-effective than a disposable system.

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Objectif : Fournir des lignes directrices pour la création et le maintien d'un programme de perfusion sous-cutanée continue de narcotiques chez les patients atteints de cancer en proie à des douleurs chroniques au moyen d'une analyse des besoins en narcotiques et de l'issue du traitement des patients à qui l'on a administré un tel régime thérapeutique et une comparaison des coûts des deux systèmes de perfusion utilisés le plus couramment.

Conception : Étude rétrospective.

Contexte : Établissement de soins tertiaires et domicile des patients.

Patients : Sur 481 patients qui ont consulté pour des douleurs causées par un cancer entre juillet 1987 et avril 1990, 60 (12 %) répondaient aux critères d'admissibilité (c.-à-d. qu'ils étaient insensibles au traitement médical type et qu'ils étaient suffisamment surveillés à domicile).

Intervention : Perfusion sous-cutanée continue de chlorhydrate d'hydromorphone ou de morphine administrée d'abord à l'hôpital et ensuite à domicile dans la mesure du possible.

Mesures des résultats : Choix des patients, besoins posologiques en narcotiques, taux de sortie, préférence des patients pour un schéma posologique d'analgésiques, effets secondaires, complications et coût-efficacité.

Résultats : La dose moyenne d'entretien de la perfusion au départ après le dosage posologique était presque trois fois supérieure à la dose nécessaire avant la perfusion (hydromorphone ou l'équivalent, 6,2 contre 2,1 mg/h). Dix-huit patients sont décédés, et on a renvoyé les 42 autres à domicile pour une moyenne de 94,4 (écart-type de 128,3) jours (extrêmes de 12 et 741 jours). En moyenne, la vitesse de perfusion maximum était de 24,1 mg/h (extrêmes de 0,5 et 180 mg/h). À une exception près, tous les patients préféraient le système de perfusion à leur ancien schéma analgésique par voie orale. Malgré d'importantes augmentations de la posologie, les nausées et les vomissements ont été bien maîtrisés dans tous les cas. Douze patients (20 %) ont subi de graves effets toxiques systémiques ou des complications; six sont devenus encéphalopathiques, ce qui a nécessité une réduction de la posologie, cinq étaient atteints d'infection sous-cutanée nécessitant une antibiothérapie, et un souffrait de dépression respiratoire. La pompe à perfusion programmable s'est révélée beaucoup plus rentable que le dispositif de perfusion jetable une fois atteint un seuil de rentabilité de 8 mois.

Conclusions : La perfusion sous-cutanée continue d'opioïdes au moyen d'une pompe portative et programmable est sécuritaire et efficace chez certains patients insensibles au traitement médical type de douleurs attribuables au cancer. Le dosage posologique peut nécessiter l'accroissement rapide de la posologie, mais on la tolère généralement bien. Dans la plupart des collectivités qui entreprennent un tel programme, un système de perfusion programmable sera plus rentable qu'un système jetable.

Narcotic analgesics provide the basic pillar of management of cancer pain. Almost 35% of patients undergoing active therapy and 60% to 90% of those with advanced disease require an opioid analgesic to control pain.[1] Although adequate relief can be provided in 80% to 90% of cases through the judicious use of oral narcotic and adjuvant analgesic therapies,[2,3] narcotic-related side effects are common and represent a major limiting factor in maintaining quality of life.[4] A continuous parenteral infusion device can be used in cases of uncontrolled pain and unacceptable side effects because it provides stable blood levels of the infused drug that can be titrated to the needs of each patient. Thus, the peak-level sedation and trough-level breakthrough pain associated with intermittent dosage regimens may be avoided. The other main advantage of continuous parenteral infusion is that it bypasses the stomach; this is obviously advantageous for patients with intractable nausea and vomiting or a nonfunctional gastrointestinal tract.

The continuous subcutaneous infusion of narcotic analgesics has largely taken over from continuous intravenous infusion, because the former technique allows for infusion into the chest wall or abdomen in an ambulatory patient.[5-8] With the availability of portable infusion pumps people can be managed on an outpatient basis without the need for intravenous access. In addition, a recent randomized double-blind trial showed that there was no significant difference in the analgesic or side-effect profiles between continuous subcutaneous and intravenous infusion of hydromorphone in the management of cancer pain.[9]

We analysed the narcotic requirements and treatment outcome of 60 cancer patients who required continuous subcutaneous narcotic infusion. We also compared the operating costs of two com-

monly used infusion devices: a programmable computerized pump and a disposable apparatus. We specifically addressed these issues to provide guidelines for the institution and maintenance of a continuous subcutaneous narcotic infusion program for patients with chronic cancer pain.

Methods

Between July 1987 and April 1990 continuous subcutaneous infusion of either hydromorphone hydrochloride (Dilaudid) or morphine sulfate was started in 60 (12%) of 481 patients seen in neuro-oncologic consultation for cancer pain. These patients were initially seen at the London Regional Cancer Centre or on the oncology wards of the Victoria Hospital Corporation, the affiliated teaching hospital of the University of Western Ontario, London. A portable programmable computerized pump (CADD-PCA [Pharmacia (Canada) Inc.]) and a 27-gauge needle (Sub-Q-Set; Baxter Healthcare, Hooksett, NH) were used on an inpatient basis so that appropriate investigations could be done in concert with dose titration and education of the patient and family. In addition to having uncontrolled pain many of the patients were drowsy or confused or had nausea and vomiting. Therefore, to establish whether their symptoms were due to the analgesic regimen or the underlying cancer these patients routinely underwent metabolic screening and radiologic studies to determine the extent of the disease if further radiotherapy was thought to be beneficial.

Entry criteria

The 60 patients were eligible because they met one or more of the following criteria.

- Patients with functional gastrointestinal tracts in whom adequate trials of at least two major orally administered narcotic analgesics (usually hydromorphone and morphine) combined with the appropriate use of non-narcotic analgesics such as nonsteroidal anti-inflammatory drugs had failed (i.e., had not adequately relieved pain despite dose escalation according to standard pharmacologic principles[1] until narcotic-related side effects became unacceptable).
- Patients unable to receive oral opioid therapy because of dysphagia or intractable nausea and vomiting due to bowel obstruction or some other visceral pain syndrome.
- Terminal patients in the last few hours or days of life who are no longer able to receive medications orally and in whom rectal administration of narcotic analgesics is inappropriate.
- Patients whose very high oral opioid requirements, usually in excess of 30 tablets per day, are perceived as a burden to the patient and family.
- Patients being discharged home who have a family member or significant other who lives with them and is able to learn the operation of the infusion pump and monitor its use.

Patients with primarily neuropathic pain or pain related to movement (incident pain) were usually excluded, because these pain syndromes generally respond poorly to narcotic analgesics.[4,10,11]

Dosing guidelines

Continuous subcutaneous infusion was usually started at a dose equivalent to the patient's previous oral narcotic intake (i.e., the infusion dose over 24 hours was equivalent to the oral dose over the same time interval). The dose was increased by 25% to 50% every 24 to 48 hours as required until the pain was under control or side effects limited further increases.[12] For conversion between oral and subcutaneous doses of morphine a relative potency ratio of 3:1 (i.e., 30 mg of morphine given orally was considered equivalent to 10 mg given subcutaneously) was used, since recent information indicated that orally administered morphine becomes more potent with repeated doses because of accumulation of an active metabolite.[13,14] In addition, the infusion pump was programmed to deliver supplemental bolus doses for breakthrough pain to add a component of patient-controlled analgesia. Bolus doses were usually 50% of the hourly infusion dose and set for a maximum of 60-minute intervals. Dose titration was usually completed by day 5 but occasionally required 7 days. For comparisons of the analgesic requirements before and after the start of infusion, day 7 was chosen as the day representing the initial maintenance infusion dose (i.e., the dose that provided maximum pain relief with minimum side effects).

Hydromorphone was often selected because of its relatively high potency (five to six times that of morphine)[1] and solubility (300 mg/mL).[15] Doses were expressed as subcutaneous hydromorphone or equivalent according to standard relative analgesic potency estimates[1] in order to compare oral and subcutaneous doses of morphine and hydromorphone.

Patient follow-up and outcome measures

All patients receiving continuous subcutaneous infusion were followed up by the palliative care team, which comprised a physician, two nurses, a pharmacist and a social worker. About half the patients resided in Middlesex County, and the other half were from various parts of southwestern Ontario. The nurses were primarily responsible for educat-

ing the patients and their families on the rationale and function of the infusion pump. The designated supervisor at home was taught how to change needles and how to operate the pump so that doses could be altered at home on the advice of a physician. The injection site was changed about every 7 days.[8,10] Regular telephone contact was maintained, and patients were seen in the outpatient clinic about every 4 weeks, sometimes more or less frequently depending on their clinical problems and the distance to be travelled. Patients living in Middlesex County were usually visited weekly by the palliative care nurses, but we also relied on nurses in the Ministry of Health's Home Care Program as well as family physicians for day-to-day supervision. Most of the home care nurses in our catchment area were trained in the technique of continuous subcutaneous infusion and were familiar with the infusion apparatus. Most of the family physicians maintained an active role in patient management. A physician from the London Regional Cancer Centre was available at all times to intercept problems arising during infusions. Each patient was followed until death or until the infusion therapy was stopped.

Patients were asked to state their preference between continuous subcutaneous infusion and their previous analgesic regimen once they reached the initial maintenance infusion dose. Quantitative scales of pain intensity and side effects were not considered useful because of the open, uncontrolled study design. However, side effects were noted. Significant complications (systemic toxic effects necessitating dose reduction and local infection necessitating antibiotic treatment) were documented. The frequency of readmission because of poor pain control and the requirement for more invasive procedures such as percutaneous cordotomy were also used as outcome measures to assess the efficacy of the infusion therapy.

Cost analysis

The analgesic research nurse and the Pharmacy Department kept detailed records of narcotic dose requirements and supplies for continuous subcutaneous infusion. To compare the operating costs per patient of the programmable computerized infusion pump and the disposable infusion apparatus (Travenol Infusor; Travenol Laboratories Inc., Deerfield, Ill.) we used the following formula.

$$y = (\text{cost/d})x$$

where y is the total cost and x the number of infusion days.

For treatment with the programmable pump we added the initial purchase cost of $3800. During the study period the patients were treated for a total of 4204 patient-days. During this time 1276 drug cassettes were used, at a cost of $28.15 each on average. The pharmacist's time for preparing each drug cassette was estimated to be 15 minutes, at $30 per hour. We estimated that the total nursing time required for education was 5 hours per patient, at $25 per hour. This included brief updates once the patient was discharged from hospital. The cost of maintaining the infusion pump was about $1200. The total costs for nursing and pharmacy services, supplies and maintenance were then divided by the 4204 patient-days to obtain the average cost of each of these items per patient-day.

The disposable infusion apparatus, an alternative to the programmable pump, is discarded every 24 hours. It is an elastomeric balloon pump that infuses 48 mL/d at a fixed rate of 2 mL/h. This requires the drug concentration to be adjusted to this flow rate to meet the patient's narcotic requirements. We estimated what our costs would have been for the disposable apparatus from our experience with Travenol Infusors before July 1987. The pharmacist's time to prepare each infusor on a daily basis was about 20 minutes. Nursing time for education was estimated at 2 hours per patient. Each infusor costs about $19.

Physician, hospital, drug and home-care costs were not included in the analysis because they were equivalent for each infusion system.

Results

The mean age of the patients was 52 (standard deviation [SD] 12) years. Table 1 shows the other characteristics. Fifty-four (90%) had already received

Table 1: Characteristics of 60 cancer patients who underwent continuous subcutaneous narcotic infusion to control chronic pain

Characteristic	No. (and %) of patients
Sex	
Male	31 (52)
Female	29 (48)
Site of primary tumour	
Breast	14 (23)
Lung	13 (22)
Gastrointestinal tract	12 (20)
Genitourinary tract	8 (13)
Other	13 (22)
Main pain syndrome (due to tumour infiltration)	
Bone	13 (22)
Soft tissue	13 (22)
Visceral	13 (22)
Bone and soft tissue	10 (17)
Nerve	6 (10)
Bone and nerve	5 (8)

at least one course of radiotherapy, and 29 (48%) had received chemotherapy or hormonal therapy.

Table 2 shows the indications for the continuous subcutaneous infusion. All of the patients had poor pain control except for the few who were near death or had very high oral narcotic requirements. In all, 52 patients received hydromorphone and 8 morphine. Four of the latter patients were subsequently given hydromorphone to minimize the infusion volume and to maximize the longevity of each drug cassette.

The mean initial maintenance dose was almost three times the dose required before infusion was started (hydromorphone or equivalent 6.2 [SD 9.0] v. 2.1 [SD 1.8] mg/h). Three patients required a maintenance dose that was at least eight times the preinfusion dose; only four required a maintenance dose that was less than the preinfusion dose. The mean maximum infusion dose of hydromorphone or equivalent was 24.1 (SD 36.7) mg/h (extremes 0.5 and 180 mg/h). The concentration of hydromorphone used in the pump cassettes varied from 1 to 150 mg/mL. The mean daily increase in dose[10] was 9.3% (SD 12.3%) of the initial dose (extremes 0% and 55%).

Treatment outcome

The overall mean duration of infusion treatment was 68.2 (SD 113.1) days. Eighteen patients died in hospital, and the remaining 42 were discharged home and continued the infusion therapy for a mean of 94.4 (SD 128.3) days (extremes 12 and 741 days). All but one of the patients and their families preferred the infusion therapy to their previous oral analgesic regimen; one had no preference. Despite major dose escalation after the infusion was started, nausea and vomiting were well controlled in all patients (metoclopramide, 40 mg/d, was added to the infusion dose in two cases); sedation did not develop as a new side effect in any patient who had not had it before infusion.

Table 2: Indications for the continuous subcutaneous infusion

Indication	No. (and %) of patients
Unacceptable side effects from oral narcotic therapy	35 (58)
Altered mental status	15 (43)
Nausea and vomiting	12 (34)
Both	8 (23)
Nausea and vomiting due to visceral pain syndrome	11 (18)
Terminal illness*	7 (12)
Large oral dose of narcotic required	4 (7)
Dysphagia	3 (5)

*Patients in the last few hours or days of life who were unable to receive oral therapy and in whom the use of rectal suppositories was inappropriate.

Indirect evidence of analgesic efficacy and improved quality of life was indicated: 42 of the patients were discharged home, and only 12 had to be readmitted because of poor pain control or unacceptable side effects from the infusion therapy. Several of these patients underwent neuroablative procedures such as percutaneous cordotomy or intrathecal phenol neurolysis;[16] this allowed seven to be weaned from the narcotic infusion and receive opioid drugs orally again. Two patients were readmitted with severe pain and never regained good pain control despite major increases in their narcotic infusion doses.

In all, 12 (20%) of the patients experienced serious systemic toxic effects or complications. Six became quite confused and had myoclonus; they required dose reduction, and some went on to have a neuroablative procedure. A subcutaneous infection necessitating antibiotic treatment developed in five patients. In one of these cases a central venous catheter was required for continuous intravenous infusion. The drug concentration may have been a factor in these infections, because three patients were receiving relatively high concentrations of hydromorphone (20 mg/mL or more). Finally, respiratory depression developed in one patient during dose titration and necessitated intravenous naloxone therapy.

Cost analysis

The average cost per patient-day to operate the programmable infusion system was $14.44 (Table 3). The average cost of the disposable system was more than double ($30.56), but the initial purchase of a programmable pump was not required. Fig. 1 compares the costs per patient-day of the two infusion systems. The total cost of the programmable pump was $\$14.44x + \$3800$; the corresponding cost for the disposable infusor was $\$30.56x$. Although there was an initial cost of $3800 to purchase the programmable pump, the break-even point was 236 days, after which the programmable pump system became more cost-effective than the disposable system.

Discussion

The retrospective, nonblind nature of our study design limits the usefulness of the data regarding treatment outcome. Two other series involving more than 160 patients were designed in a similar fashion, and each concluded that continuous subcutaneous infusion of opioid drugs is safe and effective for the management of cancer pain.[10,17] A single prospective

crossover trial comparing continuous subcutaneous morphine infusion and conventional intermittent oral or subcutaneous morphine administration found that the former technique significantly improved pain control and was associated with fewer incidents of nausea, sedation and constipation.[18] However, the trial used a nonblind design. From our findings and the results of these reports the conclusion that subcutaneous narcotic infusion for cancer pain is safe and effective seems valid and may have to suffice. A randomized controlled blind trial comparing subcutaneous and oral routes in patients with poorly controlled pain and side effects would be difficult to design and probably unethical.

What does our study add to the extant literature? The observation that 59 of the 60 patients preferred the infusion therapy to their previous analgesic regimen is hardly surprising, because many of the patients could no longer tolerate drugs orally and because the initial maintenance infusion dose was three times the dose before infusion on average. However, what was striking and not previously reported was the magnitude of dose escalation above oral doses over a matter of days and the fact that these high doses were tolerated by most of the patients. This impressive flexibility in opioid dosing illustrates the value of avoiding the gastrointestinal tract and shows the utility of maintaining blood narcotic levels within a narrow therapeutic range to avoid side effects associated with intermittent dosing.[18] The benign outcome of rapid dose escalation should also allay the anxiety that many physicians feel about the risk of respiratory depression. Serious respiratory depression is extremely uncommon in opioid-tolerant patients; it was seen in only one of our patients and complicated the management of only 1% of the patients in the study by Bruera and associates.[10] Our patients were even more tolerant to narcotic analgesics than those in the latter study. Our mean daily dose increase and maximum infusion rate were 9.3% and 24.1 mg/h respectively, as compared with 2.4% and 12.7 mg/h in the study by Bruera and associates.

Our finding that only 12% of the patients seen in consultation for cancer pain were eligible for continuous subcutaneous infusion illustrates the selective nature of this technique. Many of these patients were referred for consideration of subcutaneous narcotic infusion. Oral drug delivery is always preferred, and most patients can be managed by means of adjusting oral narcotic and adjuvant analgesic doses.[1] We strictly adhered to our inclusion criteria and tended to exclude patients with neuropathic and incident pain because of their relative unresponsiveness to narcotic analgesics.[4,10,11] Therefore, neuropathic pain due to tumour infiltration of nerves is underrepresented in the pain syndromes indicated in Table 1.

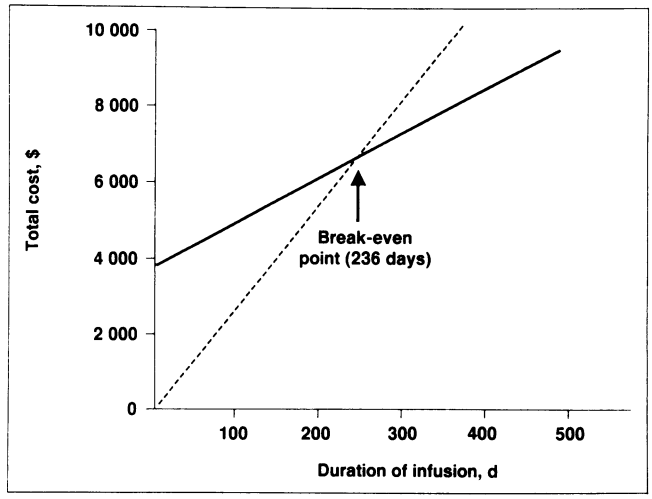

Fig. 1: Costs per patient-day of portable programmable computerized narcotic infusion pump (solid line) and disposable narcotic infusion device (broken line) for patients with chronic cancer pain. Initial cost of programmable pump was estimated to be $3800.

Table 3: Average cost per patient-day of the two infusion systems

	System; cost, $	
Service	Programmable	Disposable
Education of patients and families by nurses	1.78	0.71
Pharmacy (drug preparation)	2.28	10.00
Supplies		
Drug cassettes	8.54	–
Disposable infusor	–	19.00
Extension tubing and needles	0.85	0.85
Batteries	0.71	–
Maintenance	0.28	–
Total	14.44	30.56

Many patients with incident pain have pathological fractures that have not responded to radiotherapy and are not amenable to surgical stabilization. Incident pain of this type represents a major challenge in the management of cancer pain.

Two cost analyses involving patients with cancer pain have shown that the mean daily cost of continuous subcutaneous infusion on an outpatient basis is less than half the cost of inpatient infusion therapy.[10,19] One of the studies[10] involved the Travenol Infusor and the other[19] the Pharmacia portable infusion pump. Given that outpatient management is more cost-effective we have further shown that the use of a portable programmable infusion pump is more cost-effective than the use of a disposable device in a program that is active for more than 8 months. However, we assumed that the programmable pump would be used continuously, without any "down time." In reality it is often necessary to purchase at least one extra pump to allow for variable demand. The cost of the programmable pump system then becomes $\$14.44x + \$7600$, such that the break-even point is extended to about 16 months. With the capability of programming bolus doses for breakthrough pain outpatients have the added benefit of patient-controlled analgesia,[20] which may decrease the need for physician and nursing intervention. There are now other portable programmable infusion pumps on the market, so the cost of these devices may come down.

Given the economic necessity of outpatient management whenever feasible, many medical communities are now embarking on a subcutaneous narcotic infusion program or are seriously considering it. Subcutaneous infusion of opioid drugs with the use of a portable programmable pump is safe and effective in selected patients who have failed to respond to standard medical management of cancer pain. It is also cost-effective because of its use in the outpatient environment. However, these programs require a major commitment from physicians, palliative care nurses, pharmacists and home care personnel. The management of cancer pain with the use of a programmable infusion pump provides an excellent example of how we can use new technology to shift the burden of care from the hospital to the community in order to improve quality of life and decrease health care costs.

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