Continuous Subcutaneous Infusion of Opiates at End-of-Life

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OBJECTIVE: To review pertinent controlled trials using the continuous subcutaneous infusion of opioids (CSIO) at end-of-life and offer insight to pharmacists and clinicians into the appropriate use of this route of administration.

DATA SOURCES: A MEDLINE search for information regarding the subcutaneous administration of opioids in terminally ill patients (1975–December 2002) was conducted using the key words subcutaneous, narcotics, morphine, hydromorphone, fentanyl, pain, hospices, and palliative care. Additional references were located through review of bibliographies of the articles cited. Case reports and postsurgical studies were excluded. Searches were limited to English-language studies using humans.

STUDY SELECTION AND DATA EXTRACTION: Experimental and observational studies were evaluated, using prospective trials as the evidence base for conclusions and including pertinent retrospective trials as they relate to the subcutaneous infusion of opioids at end-of-life.

DATA SYNTHESIS: CSIO is effective and safe for use in terminal illness. Appropriate situations for consideration of CSIO are when difficulties arise in using the oral route, standard oral opiate therapy has failed adequate trials, the patient has limited intravenous access, adequate supervision of the CSIO is present, and CSIO will not unduly limit the functional activity of the patient.

CONCLUSIONS: CSIO has a proven role in the management of pain at end-of-life. CSIO should not be considered the first route for administration of opiates, but does offer distinct advantages in the appropriate setting. CSIO continues to be a choice for end-of-life patients and is gradually becoming a standard practice in palliative medicine.

KEY WORDS: fentanyl, hospices, hydromorphone, morphine, narcotics, palliative care, subcutaneous.

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End-of-life care focuses on providing patient comfort in the least invasive means. Oftentimes, as patients enter the final stages of the dying process, the preferred oral administration of opiates becomes problematic. A relatively simple technique of continuous subcutaneous infusion of opiates (CSIO) is an intervention that is easily used, permits rapid titration of opiates to the patient's needs, and has an acceptable adverse effect profile.

Relatively few articles have been published to guide clinicians in the subcutaneous infusion of opiates at end-of-life. The objectives of this article are to review pertinent controlled trials using CSIO at end-of-life and offer insight to pharmacists and other clinicians into the appropriate use of this route of administration.

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Data Sources

A MEDLINE search (1975–December 2002) related to the subcutaneous administration of opioids in terminally ill patients was conducted using the key words morphine, subcutaneous, palliative, pain, hydromorphone, fentanyl, infusion, hospices, and narcotics. Searches were limited to English-language studies using humans. Experimental and

observational studies were selected, using prospective trials as the evidence base for conclusions and including pertinent retrospective trials as they relate to the subcutaneous infusion of opioids at end-of-life. Additional references were located through review of the bibliographies of the articles cited. Case reports and postsurgical studies were excluded. Publications dated before 1975 were excluded, as the majority of such were case reports or uncontrolled trials.

Subcutaneous infusions date back to the early 20th century with the administration of fluids to pediatric patients.[1] Literature that discusses subcutaneous infusion practices in the 20th century includes many references to earlier publications about adverse effects associated with this technique. In the 1970s, palliative care physicians in the UK renewed interest in this intervention for managing terminal cancer pain.[2] In the 1990s, the first trials in the US were conducted looking at subcutaneous infusion of opiates.[3] The results of several randomized trials comparing the efficacy of CSIO with that of oral and intravenous routes of administration are now available.

Hospices across the US report widespread use of CSIO, with morphine being the most common opiate used.[4] Approximately 75% of all US-licensed hospice agencies report using CSIO, with 95% of these agencies using this technique for palliative management. CSIO is administered most frequently via a cartridge system, and larger hospices and hospices that use long-term care facilities have a significantly higher prevalence of CSIO.

Indications and Advantages of CSIO

Indications for CSIO depend largely on the patient's needs and the level of clinician expertise available.[5] Certainly, the oral route is preferred for analgesic administration. CSIO has 2 distinct advantages for patients who cannot tolerate oral administration in that it produces decreased peak/trough concentrations and the dosage is easily titrated. CSIO limits the peak concentration adverse effects of opiates, such as sedation, and lessens the trough concentration problems of breakthrough pain or dyspnea. Patients who have failed adequate trials of oral opiates, but continue to exhibit significant peak/trough adverse effects, would be appropriate for CSIO. Palliative care patients often experience swallowing-related difficulties. Whether the swallowing difficulty is significant dysphagia, intractable nausea and vomiting, or a burdensome number of medications required to maintain comfort, CSIO provides an alternative to the oral route and avoids the gastrointestinal tract in cases of bowel obstruction. Titration of opiates to meet the changing dose requirements with terminal illness can be challenging. As many of the opiates used in CSIO have short half-lives, these can be rapidly titrated to meet the patient's analgesic requirements.

Administration

The focus of care remains on the patient's comfort and optimization of function. CSIO, using a portable pump, can provide improved analgesia while maintaining freedom of mobility. In frail or bed-bound patients in whom mobility is not a significant issue, CSIO can be provided via a standard hospital infusion pump. The choice of pump depends on the patient's function and quality of life, as well as the pump's characteristics.

There are numerous infusion systems to provide CSIO. Varying pump complexity, patient/caregiver capabilities, and the nature of local resources are often factors to be considered in the choice of an appropriate CSIO pump. An excellent review of CSIO in the home setting can help in this decision.[6] Pertinent questions about pump choice to consider include:

1. Can the pump's complexity be handled by the patient/caregiver?
2. Can the pump provide a bolus or breakthrough dose?
3. Does the pump have programmability in terms of flow volume and lock-outs?
4. Does the pump provide an alarm for malfunctions?
5. What is the pump's record or documentation capabilities?

One of the simplest CSIO methods for debilitated and bed-bound patients is a 27-gauge butterfly needle with the opiate infused via a standard intravenous infusion pump. Breakthrough dosing is administered by a nurse or caregiver via the existing subcutaneous line. If the patient is more cognitively intact and functional or an involved caregiver can be recruited, a patient-controlled analgesia (PCA) pump or portable pump can be used. The PCA pump, which can provide a continuous infusion as well as bolus dosing for breakthrough pain, can also be used by a surrogate caregiver who is trained to identify signs of pain, thus putting control of pain as close to the patient as possible. Syringe drivers seem to be used less commonly due to limitations with dosing volumes and lack of breakthrough dosing capabilities.

Continuous subcutaneous infusions (CSCIs) can be applied by nursing personnel and caregivers with minimal training. Typically, a 27-gauge butterfly catheter is inserted into the subcutaneous tissue at a 45–60° angle with the surface of the skin, bevel up. The needle should rest parallel to the underlying subcutaneous tissue. Another option is to use a Teflon catheter, which has been shown to have the advantage of longer duration of site placement, thus reducing the risk of site infection.[7-9]

Site selection will depend largely on the patient's preference or care team's choice. In the confused patient, the posterior scapular area may be useful to inhibit the patient from pulling out the catheter. Otherwise, the anterior chest and abdomen are common sites, and numerous other sites such as the thigh, flank, and deltoid can be considered. Application of a clear dressing over the subcutaneous site permits visualization of the surrounding skin for signs of infection or irritation.

Insertion site care, duration, and adverse effect rates are variable. At present, there appears to be no single protocol for maintaining the subcutaneous site. Scheduled site changes every 3–7 days, or when erythema develops, appear reason-

able. Therefore, caregivers need to be familiar with the signs of infection or irritation when monitoring the site.

Dosing and Adverse Effects

Appropriate dosing with CSIO is critical to its success and differs from routine oral opiate therapy in a number of important areas. Much of the potential toxicity related to CSCIs relates to the conversion from a different opioid and route. Equianalgesic conversion of opioids is covered more thoroughly elsewhere,[10] but an important consideration in conversion of opiates is incomplete cross-tolerance. Tolerance can be defined as the need for increasing dosages to maintain the desired effect (ie, analgesia). While tolerance to the analgesic effects of opiates is not believed to be common, incomplete cross-tolerance when converting from one opiate to another can lead to distressing symptoms such as nausea and sedation in opioid-naïve patients.[11] When the patient is converted to a new opioid (eg, to subcutaneous hydromorphone from oral morphine), these common opioid adverse effects occur if the equianalgesic conversion is not reduced by 30–50%. As there is variability in the degree of incomplete cross-tolerance to these receptor-mediated opioid affects, reducing the opioid's dose by that amount will limit significant incomplete cross-tolerance adverse effects.

Table 1 describes equianalgesic doses of several opioids that can be used by the subcutaneous route.[12] Table 2 summarizes clinical pearls about opioid conversion and provides an example of conversion from oral morphine to CSIO using hydromorphone.

For conversion to CSIO, both hourly infusion and breakthrough dosages will need to be determined. The hourly infusion dosage will be determined from the equianalgesic conversion calculation, taking into account the infusion volume and incomplete cross-tolerance. A target maximum for infusion volume of 3 mL/h is reasonable. Larger infusion volumes have been tolerated for subcutaneous hydration,[13] but there appears to be few data for CSIO. Once the hourly infusion dosing and volume are determined, the breakthrough or rescue dosage should be 50% of the hourly infusion dose and can be administered as frequently as every 15 minutes because of the rapid onset of maximal analgesic benefit. This permits rapid titration of infusion opioids to meet the patient's analgesic needs. Adjustment of the hourly infusion dose, taking into account the breakthrough dosing, should not occur more frequently than every 8 hours.

Adverse effects related to CSIO are related to both the drugs' pharmacologic effects and the site of administration. Adverse effects such as sedation, constipation, and respiratory depression are associated with the pharmacology of opioids as a class, and similar reactions are expected from CSIO as with orally administered opioids. There is substantial interindividual variability in the production of metabolites of opiates, whether given orally or parenterally, and the route of administration appears to have little role in adverse effect profiles.[14] Local site irritation or erythema is common and often resolves without treatment. More significant local reactions include induration or inflammation as a result of preservatives or impurities in the infusion. Painful subcutaneous plaques may also develop and reflect subcutaneous inflammation and necrosis.[15] These plaques may recur even with site rotation and may require consideration of an alternative route of administration.

Overall, CSCIs of even highly concentrated opioid solutions appear to be well tolerated.[16] Most patients can tolerate the same site for 7 days, and patients have been maintained on subcutaneous infusions for greater than a year.

The use of hyaluronidase may contribute to problems with CSIO. Hyaluronidase is an enzyme that hydrolyzes intercellular ground substance to aid in the absorption and dispersion of injected drugs. Experience with hyaluronidase in the subcutaneous administration of opiates has shown a number of potential adverse effects including local erythema, edema, and pain, which may limit its widespread use[17-19]; other practitioners have examined the use of infusions with and without hyaluronidase and found no difference in adverse effects or patient perception of comfort.[17]

Table 1. Equianalgesic Doses[12,a]

Drug	Dose (mg)		
	Oral	Parenteral[b]	Rectal
Fentanyl		0.1–0.2	
Hydromorphone	6–7.5	1.5–2	6
Methadone	15	7.5–10	
Morphine	30–40	10	
Oxycodone	15–30		

[a]Based on single-dose studies; dose required may be lower with repeated administration.
[b]Intramuscular, intravenous, subcutaneous.

Table 2. Equianalgesic Conversion for CSIO

Clinical pearls of conversion
- Oral morphine dose is 3 times the parenteral[a] dose. Parenteral hydromorphone is 1/6 the parenteral morphine dose.
- Begin new opioid analgesic at 2/3 of the calculated equianalgesic dose due to incomplete cross-tolerance.
- Rescue/breakthrough pain doses should be 10% of the daily dose given as an immediate-release preparation.
- Always prescribe a bowel regimen using stimulant laxatives with opioid administration.

Example of conversion
- Convert 450 mg q12h of oral morphine to CSCI of hydromorphone.
- The total daily dose of oral morphine is 900 mg, equivalent to 300 mg/day of subcutaneous morphine.
- The hydromorphone dose is approximately 1/6 the subcutaneous morphine dose (50 mg/day).
- Due to incomplete cross-tolerance, hydromorphone should be started at 2/3 of the calculated equianalgesic dose (30 mg/day).
- Divide by 24 to convert daily to hourly hydromorphone dosage (1.25 mg/h).

CSCI = continuous subcutaneous infusion; CSIO = continuous subcutaneous infusion of opioids.
[a]Intramuscular, intravenous, subcutaneous.

Pharmacology

Responses to various opioid agents vary from patient to patient. Therefore, understanding pharmacokinetics and pharmacodynamics is important when individualizing drug therapy with CSIO. The following discussion of the pharmacology of the opioid agents focuses on aspects of the medications that relate to the efficacy and safety with administration via subcutaneous infusion. Morphine, hydromorphone, fentanyl, and methadone are the most common opioids administered by the subcutaneous route.

MORPHINE

Morphine is absorbed after oral administration and subcutaneous or intramuscular injection.[20] As with most opioids, the effect of a dose is less after oral than after parenteral administration due to variable, but significant, first-pass metabolism in the liver. The shape of the time–effect curve also varies with the route of administration, so that the duration of action is often somewhat longer with the oral route. The major pathway for the metabolism of morphine is conjugation with glucuronic acid. The 2 major metabolites formed are morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G), both of which can cross the blood–brain barrier and elicit significant clinical effects. M6G has similar pharmacologic effects as morphine, but is approximately twice as potent. With chronic administration, M6G accounts for a significant portion of morphine's analgesic actions, and its blood concentrations typically exceed those of morphine.

HYDROMORPHONE

Hydromorphone is a semisynthetic derivative of morphine with a very similar pharmacokinetic profile.[20] Hydromorphone is readily absorbed from the gastrointestinal tract, as well as after subcutaneous or intramuscular injection. Hydromorphone is one of the more lipid-soluble opiates; therefore, it acts more rapidly than morphine after subcutaneous administration due to faster absorption into the central nervous system.

FENTANYL

Fentanyl is a synthetic opioid that is about 100 times more potent than morphine as an analgesic.[20] Fentanyl is highly lipophilic and therefore rapidly crosses the blood–brain barrier and acts more rapidly than morphine after subcutaneous administration. Recovery from the analgesic effects of fentanyl also occurs more quickly compared with morphine. However, when larger doses are given for a prolonged period of time, fentanyl's duration of action becomes similar to that of the longer-acting opioids.

METHADONE

Methadone is a long-acting μ receptor agonist with pharmacologic properties similar to those of morphine.[20] The outstanding properties of methadone are its extended duration of action and its tendency to show persistent effects with repeated administration. Peak concentrations occur in the brain within 1–2 hours after subcutaneous or intramuscular administration and correlate well with the intensity and duration of analgesia. After repeated administration, methadone accumulates in various tissues, including the brain. When the agent is discontinued, low concentrations are maintained in the plasma by slow release from extravascular binding sites, which probably accounts for the relatively mild withdrawal syndrome. Again, being more lipid soluble with faster absorption into the central nervous system, methadone acts more rapidly than morphine after subcutaneous administration. Care must be taken when escalating the dosage because of methadone's prolonged half-life and its tendency to accumulate over a period of several days with repeated dosing. The duration of methadone's analgesic activity is similar to that of morphine after a single dose, despite its longer half-life.

Pharmacokinetic Trials of Morphine Via CSCI

In recent years, CSCI of morphine has become a viable option for patients who cannot take oral medications or who do not have intravenous access. However, few studies have been published regarding the pharmacokinetics of morphine and its metabolites given by this route. Table 3 summarizes comparative pharmacokinetic parameters of morphine, hydromorphone, fentanyl, and methadone.[12]

Wolff et al.[21] conducted a study to analyze steady-state concentrations of morphine, M3G, and M6G in the plasma and cerebrospinal fluid (CSF) in 21 cancer patients treated with subcutaneous infusion of morphine. The median treatment duration at the time of sampling was 6 days, with a median daily morphine dose of 48 mg. The authors'

Table 3. Pharmacokinetic Comparison[12,a]

Drug	Half-Life (h)	Metabolism	Peak Effect (h)	Mean Duration of Analgesia (h)
Fentanyl	1–6[b]	liver	<0.5 (im/sc)	0.5–2
Hydromorphone	2–4	liver	1.5–2 (po) 0.5–1 (im/sc)	4–5
Methadone	22–25	liver; drug may accumulate with repeated doses, producing longer duration of effect	1.5–2 (po) 0.5–1 (im/sc)	4–6
Morphine	2–3.5	liver	1.5–2 (po) 0.5–1 (im/sc)	4–7

[a]Based on single-dose studies.
[b]Analgesic effects do not correlate with half-life, but rather upon the route of administration and the distribution characteristics of the agent.

findings suggest that, during subcutaneous administration of morphine, a large interindividual variation in steady-state plasma morphine concentrations exists, with poor correlation with the daily administered dose. To some extent, a clearer correlation was found between the daily administered morphine dose and CSF concentrations. Surprisingly, the authors found no clinical evidence that concentrations of the metabolites influenced analgesia or adverse effects.

Another study compared the pharmacokinetics of morphine and morphine glucuronide metabolites after subcutaneous bolus and infusion or intravenous bolus in healthy volunteers.[14] Six volunteers randomly received morphine sulfate 5 mg by each route on 3 occasions separated by one week. Plasma samples were obtained for morphine, M6G, and M3G concentrations. The authors concluded that, although bioequivalence was demonstrated between subcutaneous bolus and intravenous administration, the data suggest that the bioavailabilities of morphine, M6G, and M3G after subcutaneous infusion were lower than after intravenous administration. This decrease in bioavailability after subcutaneous infusion may be due to failure to deliver the full dose or differences in infusion site characteristics.

Literature Review of CSIO

The following literature review includes a discussion of 2 large retrospective studies of CSIO, as well as discussion of several randomized, prospective clinical trials (Table 4).[22-30]

A retrospective review was conducted of 60 patients who had a neuro-oncologic consultation and met one or more of the following criteria to receive subcutaneous infusion: (1) failure of at least 2 major orally administered opiate analgesics, (2) unable to receive oral opioid therapy, (3) oral opioid therapy was perceived as an undue burden (typically >30 tablets per day), and (4) exclusion of neuropathic pain syndromes.[5] The objectives of the study were to provide guidelines and determine treatment outcomes and associated costs for subcutaneous opiate infusions in cancer patients with chronic pain using a programmable infusion pump and a disposable apparatus. Outcome measures included indirect measurement of discharge home for pain control and adverse effects extracted from the chart. Forty-two of the patients were discharged home, and 12 were readmitted for poor pain control. The programmable pump was more expensive unless duration of the infusion exceeded 236 days. Twenty percent (n = 12) of the patients experienced serious systemic toxic effects or complications (6 became confused and had myoclonus, 5 required antibiotic treatment for subcutaneous infection, 1 developed respiratory depression with dose escalation requiring naloxone). The authors concluded that CSIO is safe and effective for cancer pain.

Watanabe et al.[31] conducted a retrospective review of 22 inpatients with cancer pain who received subcutaneous fentanyl. The authors' objectives were to review one facility's experience with conversion to subcutaneous infusion of fentanyl. A chart review of 100-mm visual analog scale assessments of pain prior to conversion and after stabilization with subcutaneous infusion, plus other documentation of cognitive function and opioid toxicities, was performed. No significant changes in pain scales or cognitive testing were found. No local toxicities were noted, and there were subjective improvements in a number of adverse effects. The authors concluded that subcutaneous infusion of fentanyl should be considered in patients with uncontrolled pain. The study design, small sample size, and lack of statistically significant findings limit generalization.

The lack of randomized trials limits the ability to determine causality of the intervention. While end-of-life care has many challenges in performing randomized trials, the use of the crossover design can be a powerful research technique in comparing interventions, such as route of administration. The few noteworthy randomized trials shown in Table 4 provide evidence of the comparable, if not improved, pain control with CSIO compared with oral or intravenous administration. Many of the trials used a visual analog scale that permitted quantitative measurement of outcome variables. Other measures, however, lacked clear definitions or criteria for measurement and often resulted in conclusions that resulted from subjective analysis of the intervention.

Most of these studies were of relatively small sample size; sizes often appear to be convenience samples from tertiary care facilities performing the research. Sampling inadequacy and lack of patient selection criteria can affect the applicability of the findings. If these samples reflect the local referral patterns of that facility, they may not be generalizable to other facilities. On the other hand, the open selection of patients with uncontrolled pain could lead to a study population that reflects the community practice of palliative care.

Two trials included statistical errors, such as lack of power to determine differences between treatment groups.[27,29] The majority of trials included a large variation of baseline characteristics, including origin of pain. Nonvalidated scales were used in several studies for assessing pain severity and safety.[22,23,26,28] Some trials had significant drop-out rates that were not accounted for by the statistical tests used.[22,29] Design limitations included lack of specific information regarding concomitant analgesic use and adverse effects. Only one study evaluated the possibility of the development of tolerance after long-term use of CSIO.[28]

Lastly, the variable duration and venue of care may limit the conclusions that can be drawn from the data. One study was as short as 48 hours and another as long as 741 days.

CSIO was provided in a variety of settings, from the acute care hospital to the home environment, with varying degrees of technical support. Patients in the acute setting were monitored more closely by skilled personnel, which may have accounted for improved identification of adverse effects. The varying venues of care likely resulted in different practice standards, such as infusion site duration. In the home environment, the infusion site may be changed only when it becomes problematic, whereas in the acute setting, protocol may dictate site changes. Inconsistent reporting of site maintenance practices limits conclusions about infusion site adverse effects and may explain the diversity of findings.

Table 4. Prospective Clinical Trials

Trial	Design/ Objective	Outcome Measures	Results	Adverse Effects	Conclusions
Hunt et al. (1999)[22]	R, DB, crossover compare efficacy and safety of sc morphine with that of sc fentanyl in hospice cancer pts. 3 days of morphine or fentanyl (group 1), then 3 days of alternate agent (group 2); no washout period	primary pain score (0–10) and nausea score (0–10) by interview; N of breakthrough doses secondary mental status measured by the Saskatoon Delirium checklist; trail-making and semantic fluency tests; preference of opioid	no difference in pain scores; group 1 pts. on fentanyl had more breakthrough doses on days 2 and 3 ($p = 0.025$); no difference in Saskatoon Delirium scores, semantic fluency, or trail-making; 9 pts. had no preference, 4 preferred morphine, 6 preferred fentanyl; data not available for 4 pts.	no difference in nausea prevalence; difference in N of BMs during days 4–6, with group 2 fentanyl pts. demonstrating more BMs than group 2 morphine pts. ($p = 0.015$)	sc fentanyl is effective in hospice pts. with cancer and appears less constipating than morphine
Miller et al. (1999)[23]	72 pts. DB, R, C compare analgesic efficacy and adverse effects of hydromorphone and morphine via CSCI over 3 days; in 60 pts., analgesia was assessed by proxy staff using internally designed instrument that included 5 symptoms observed and 3 VAS values	primary Memorial Pain Assessment card; checklist of opioid-related adverse effects before infusion and 24, 48, and 72 h after infusion was begun	hydromorphone group more likely to require additional breakthrough in 1st 24 h with no difference in analgesic efficacy	narrative report of a "small" number of adverse effects with no difference between groups	hydromorphone is at least as effective as morphine when administered via CSCI; hydromorphone to morphine potency ratio of 1:5 may be too low
Nelson et al. (1997)[24]	40 pts. within pt., one-way crossover compare dose, efficacy, and adverse effects of iv morphine with sc morphine over 4 days	primary VAS, pain self-report scale (0–3 categorical scale), and N of breakthrough doses	32 pts. achieved stable dosing and similar efficacy for both the iv and sc morphine infusions; 8 pts. required dose escalation after institution of sc infusion, and effective analgesia was maintained	high incidence of constipation and xerostomia (21–25 pts. experienced both); 2 pts. developed local toxicity at the infusion site requiring site change	iv and CSCI of morphine are equianalgesic for most pts. and have similar efficacy and safety
Kalso et al. (1996)[25]	10 pts. R, DB, crossover assess whether epidural morphine has advantages over sc route in management of severe cancer pain over 7 days	primary pts. reported pain and adverse effects as estimated on a 100-mm VAS	no difference in reports of pain between sc and epidural routes; both routes showed improved pain control over po morphine	sc route group developed more nightmares and adverse effects when aggregated vs epidural route	no substantial benefits in terms of pain management or adverse effects between routes; sc preferred because of simplicity and lower costs
Vanier et al. (1993)[26]	8 pts. pilot, R, DB, crossover evaluate effectiveness and safety of CSCI hydromorphone and basal rate SCI + PCA in cancer pain over 4 days 48-h CSCI of hydromorphone (mode A), then 48-h continuous basal rate SCI + PCA (mode B); no washout period	primary mean pain intensity; mean dose of hydromorphone; mean N doses received by PCA	no difference in mean pain intensity difference in mean dose of hydromorphone: mode A 56.3 vs mode B 39.5 mg ($p = 0.001$) difference in mean N doses received by PCA: mode A 6.3 vs mode B 9.9 ($p = 0.03$)	marked discomfort with hydromorphone in mode B by subjective questioning; no difference in respiratory depression or sedation	demonstrated both effectiveness and safety of both modes

BM = bowel movement; C = controlled; CSCI = continuous subcutaneous infusion; DB = double-blind; PCA = patient-controlled analgesia; R = randomized; VAS = visual analog scale.

(continued on page 1021)

Role of CSIO

CSIO continues to be a choice for end-of-life patients and is gradually becoming a part of the standard of practice in palliative medicine. CSIO has both benefits and disadvantages. Significant advantages over the use of intermittent subcutaneous, intramuscular, or intravenous routes include avoidance of repetitive injections, avoidance of placement of intravenous line, freedom from delays in pain medication administration, provision of a continuous serum concentration of the drug, avoidance of adverse effects occurring at high peak concentrations and breakthrough pain at trough concentrations, and allowance of greater patient mobility.[32]

Barriers do exist at local levels for the use of CSIO. As with all opiates, many clinicians will have disproportionate concern about adverse effects and fear of addiction. Clinicians will need to assess patients for pain, be comfortable with using opiates, and in select cases, use CSIO to provide symptom relief. Another potential barrier is the variability of equipment used for CSIO at different facilities. Clinicians could encounter varying types of equipment among the agencies that serve his or her practice area. The use of CSIO should be anticipated to account for a small percentage of pain management patients. CSIO in the home could permit the patient to be maintained in the environment of choice, as well as avoid costly hospitaliza-

Table 4. Prospective Clinical Trials (continued)

Trial	Design/ Objective	Outcome Measures	Results	Adverse Effects	Conclusions
Moulin et al. (1991)[27]	15 pts. R, DB, DD, crossover compare safety and efficacy of CSCI and iv infusion of hydromorphone for chronic cancer pain over 5 days two 48-h infusions of hydromorphone sc or iv; 24-h washout with morphine	primary pain intensity, pain relief, mood, sedation measured by VAS secondary N breakthrough morphine injections; plasma hydromorphone concentrations; bioavailability	no difference in primary outcome measures after 48-h period ($p > 0.1$); no difference in N breakthrough morphine injections; significant difference in hydromorphone plasma concentrations at 48 h ($p = 0.05$); mean bioavailability from CSCI 78% that of iv ($p = 0.02$)	3 pts. with nausea during both infusions; 1 pt. with nausea only during CSCI	continuous iv infusion should be abandoned except in pts. intolerant of CSCI due to technical advantages and cost-effectiveness of CSCI
Lang et al. (1991)[28]	36 pts. prospective, intra-individually controlled compare safety and efficacy of CSCI morphine vs conventional intermittent po or sc morphine 28 inpatients received CSCI for 2–42 days; 8 outpatients received CSCI for 49–197 days	primary pain severity measured by Dewi–Rees scale daily for inpatients and weekly for outpatients; general QOL measured by Marks & Sachar scale weekly for both groups	CSCI improved pain severity and QOL to a greater extent than intermittent therapy ($p < 0.001$); CSCI vs intermittent required lower doses ($p < 0.001$)	3 pts. developed constipation, which was relieved by addition of laxatives; signs of tolerance in 2 pts. were reversed by 2 wk of methadone (opioid rotation)	low-dose CSCI of morphine is safe and effective for severe terminal cancer pain
Bruera et al. (1988)[29]	22 pts. R, crossover compare efficacy and safety of CSCI hydromorphone vs PCI in cancer pain for 6 days 3 days of CSCI or PCI hydromorphone; no washout	primary pain intensity measured by VAS; total dose; N of extra doses (prn); pt. preference	no difference in pain intensity or total dose; total N of extra doses was 6 ± 7 with CSCI vs 2 ± 3 with PCI ($p = 0.007$)	no difference in adverse effects	both methods similar in effectiveness and safety in short-term hospital use for pain control in cancer pts.
Kerr et al. (1988)[30]	18 pts. case series of pts. with uncontrolled cancer pain or those experiencing significant adverse effects or were unable to take po drugs determine the feasibility and safety of outpatient CSCI of opiates (with bolus capabilities) in pts. with cancer pain	primary VAS (0–5) via telephone follow-up	improved pain control, improved functional status, few adverse events	limited sedation and 1 seizure in a pt. receiving meperidine	pts. can maintain and control sc infusions of opiates in the outpatient setting for extended periods with improved pain control and function

CSCI = continuous subcutaneous infusion; DB = double-blind; DD = double-dummy; PCI = patient-controlled infusion; QOL = quality of life; R = randomized; VAS = visual analog scale.

tion. With the advancements in pump technology, patients will be provided fewer restrictions and better mobility.

Future Directions

Several other opioid and nonopioid agents given by CSCI have been studied. Noda et al.[33] conducted a trial in Japan evaluating the efficacy of CSCI of buprenorphine in 30 patients with severe cancer pain. The authors concluded that an infusion rate of 4 µg/kg/day following an intramuscular dose of 0.004 µg/kg provided adequate pain relief without serious adverse effects. Further studies using this potent, long-acting opioid are expected. A prospective, nonrandomized trial evaluated the efficacy of salmon calcitonin in controlling pain related to bone metastases in 22 cancer patients.[34] Pain control was initially achieved by CSCI of morphine; salmon calcitonin 400 IU/day was then subcutaneously infused adjunctively. The results suggested that high-dose infusion of salmon calcitonin may be an effective adjuvant to CSCI of morphine for treatment of metastatic bone pain. Several case reports and case series using this administration have also been conducted with other analgesics and anesthetics such as ketorolac, ketamine, and midazolam. Controlled trials are necessary to determine the role of these agents when infused subcutaneously.

Summary

After critical evaluation of clinical trials, case series, and retrospective studies, it can be concluded that CSIO is effective and safe for use in terminal illness. Appropriate situations for consideration of CSIO are when difficulties arise in using the oral route, standard oral opiate therapy has failed adequate trials, the patient has limited intravenous access, adequate supervision of the CSIO is present, and CSIO will not unduly limit the functional activity of the patient.

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EXTRACTO

OBJETIVO: Repasar estudios controlados pertinentes donde se utiliza la infusión subcutánea continua de opiatos (ISCO) en pacientes terminales y ofrecer ideas, a los farmacéuticos y a los médicos, sobre el uso apropiado de esta vía de administración.

FUENTES DE INFORMACIÓN: Se realizó una búsqueda en MEDLINE sobre la administración subcutánea de opiatos en pacientes terminales, entre los años 1975 y 2002, utilizando las palabras claves subcutáneos, narcóticos, morfina, hidromorfona, fentanil, dolor, hospicios, y cuidado paliativo. Referencias adicionales fueron localizadas a través de la revisión de las bibliografías de los artículos citados. Las búsquedas se limitaron al idioma inglés y a sujetos humanos. La literatura post-quirúrgica y los reportes de casos fueron excluídos.

SELECCIÓN DE FUENTES Y MÉTODO DE EXTRACCIÓN DE INFORMACIÓN: Las fuentes incluyeron estudios experimentales y de observación usando pruebas prospectivas como la base de evidencia para las conclusiones, e incluyendo pruebas retrospectivas pertinentes según éstas se relacionan a la infusión subcutánea de opiatos en condiciones terminales.

SÍNTESIS: La ISCO es efectiva y segura en enfermedades terminales. Situaciones apropiadas donde se debe considerar el uso de ISCO son cuando ocurren dificultades con el uso de la vía oral, cuando la terapia oral estándar con opiatos no ha pasado las pruebas adecuadas, cuando el paciente tiene un acceso intravenoso limitado, cuando existe la adecuada supervisión de la ISCO, y cuando la ISCO no limitará excesivamente la actividad funcional del paciente.

CONCLUSIONES: La ISCO tiene un rol comprobado en el manejo del dolor en condiciones terminales. La ISCO no se debe considerar la primera vía de administración de opiatos, pero ofrece definidas ventajas en la situación apropiada. La ISCO continúa siendo una opción para pacientes terminales, y poco a poco se está convirtiendo en una práctica estándar en la medicina paliativa.

Brenda R Morand

RÉSUMÉ

OBJECTIFS: Faire le point sur les essais contrôlés pertinents sur l'utilisation de la perfusion sous-cutanée continue d'opiacés en fin de vie, et donner aux pharmaciens et cliniciens un aperçu de l'usage approprié de cette voie d'administration.

SOURCES DE DONNÉES: Une recherche MEDLINE sur l'administration sous-cutanée d'opiacés chez des patients en phase terminale, sur les années 1975 à 2002, a été réalisée en utilisant les mots-clés sous-cutanée, stupéfiants, morphine, hydromorphone, fentanyl, douleur, et soins palliatifs. Des références complémentaires ont été retrouvées à partir des bibliographies des articles cités. Les études de cas et les publications relatives au post-opératoire ont été exclues. Les recherches ont été limitées aux publications en anglais et chez l'homme.

SÉLECTION DES ÉTUDES ET EXTRACTION DES DONNÉES: Etudes expérimentales et observationnelles, basées sur des essais prospectifs pour les niveaux de preuve des résultats, en incluant les essais rétrospectifs pertinents se rapportant à la perfusion sous-cutanée d'opiacés en fin de vie.

SYNTHÈSE DES DONNÉES: La perfusion sous-cutanée continue d'opiacés (CSIO) est efficace et sure d'emploi en phase terminale. Les situations justifiant de considérer le recours à la CSIO concernent les difficultés à utiliser la voie orale, l'échec de la thérapeutique habituelle par voie orale, les patients ayant un accès veineux limité, lorsqu'une surveillance adéquate de la CSIO est possible, et que la CSIO ne compromet pas l'activité fonctionnelle du patient.

CONCLUSIONS: La CSIO a un rôle établi dans la prise en charge de la douleur en fin de vie. La CSIO ne doit pas être considérée d'emblée pour l'administration des opiacés, mais elle présente des avantages spécifiques dans un environnement approprié. La CSIO reste une alternative pour les patients en fin de vie et devient progressivement une pratique standard en soins palliatifs.

Michel Le Duff