Alternate Routes for Home Opioid Therapy

Cancer causes the death of more than 54,000 Canadians and 500,000 Americans every year. Most of these patients develop significant pain before death. In these patients, the oral route for drugs is preferable because it is safe, effective, and convenient. It makes home management more simple. However, about 70% of patients will benefit from the use of an alternate (ie, nonoral) route for opioid administration for hours to months before death.2,4 When alternate routes of administration are required, “by-the-clock” intramuscular or intravenous injections can control cancer pain in most cases.4,5 However, because of the short duration of action of most opioids, injections need to be repeated regularly, usually at intervals of four hours or less. This method is ultimately undesirable because it becomes painful for the patient, time consuming for the caregivers, and difficult to maintain in the home setting.

A number of recent studies have explored alternate routes of opioid delivery. Typical starting doses of opioids for moderate to severe pain are given in Table 1. Our ability to deliver systemic opioids safely

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approximate equianalgesic oral dose</th>
<th>Approximate equianalgesic parenteral dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>30 mg q 3-4 hr (around-the-clock dosing)</td>
<td>10 mg q 3-4 hr</td>
</tr>
<tr>
<td></td>
<td>90 mg q 3-4 hr (single dose or intermittent dosing)</td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>120 mg q 3-4 hr</td>
<td>75 mg q 3-4 hr</td>
</tr>
<tr>
<td>Hydromorphone (Dilaudid)</td>
<td>7.5 mg q 3-4 hr</td>
<td>1.5 mg q 3-4 hr</td>
</tr>
<tr>
<td>Hydromorphone (in Lorcet, Lortab, Vicodin, others)</td>
<td>30 mg q 3-4 hr</td>
<td>Not available</td>
</tr>
<tr>
<td>Levorphanol (Levo-Dromoran)</td>
<td>4 mg q 6-8 hr</td>
<td>2 mg q 6-8 hr</td>
</tr>
<tr>
<td>Meperidine (Demerol)</td>
<td>300 mg q 2-3 hr</td>
<td>100 mg q 3 hr</td>
</tr>
<tr>
<td>Methadone (Dolophine, others)</td>
<td>20 mg q 6-8 hr</td>
<td>10 mg q 6-8 hr</td>
</tr>
<tr>
<td>Oxycodone (Roxicodone, also in Percocet, Percodan, Tylox, others)</td>
<td>30 mg q 3-4 hr</td>
<td>Not available</td>
</tr>
<tr>
<td>Oxydone (Numorphan)</td>
<td>Not available</td>
<td>1 mg q 3-4 hr</td>
</tr>
</tbody>
</table>

Table 1
“Our ability to deliver systemic opioids safely using alternate routes is the single most important development in home management of cancer pain.”

using alternate routes is the single most important development in home management of cancer pain.

Subcutaneous Route

In 1979, Russell described a method for subcutaneous (SC) administration of morphine to patients with advanced symptomatic cancer. Since then, a number of studies have defined this route as an effective alternative to oral opioid administration. SC administration of opioids is safe and effective. Blood levels of opioids during SC administration are comparable to those obtained during intravenous administration (Figure 1). A single SC infusion site can be used for approximately seven days. The SC route can also be used for patient-controlled analgesia (PCA) using portable pumps. Cognitive failure, frequently present in preterminal patients, renders self-administration unreliable, necessitating greater involvement of family members. Patients with a history of substance abuse may be poor candidates for PCA.

Most clinical reports of SC opioid administration have used morphine, hydromorphone, or diamorphine. These drugs all have short half-lives and hence reach steady-state plasma levels rapidly. Drugs with longer half-lives, such as methadone and levorphanol, have also been used but may be less effective at the onset of treatment and carry a hazard of delayed toxicity days after the infusion has started due to slow accumulation—a risk that is increased in elderly patients. For these reasons, drugs with relatively short half-lives (e.g., morphine) should be the first choice for SC administration.

Once the proper drug and dosage have been determined, the infusion is started using a 25- or 27-gauge butterfly needle inserted in the anterior chest or abdomen (Figure 2). A three-way stopcock is helpful for administration of extra doses of opioids, as well as for the administration of glucocorticoids or metoclopramide, if required. Infusions can be made with a portable pump or nonportable device (IVAC or IMED). Our data suggest that the rate of infusion can be increased up to 10 cc/hr without producing pain at the site of infusion.

Clysis: Pain Relief Plus Rehydration

When hydration is needed in addition to opioid administration, hypodermoclysis can be used by adding the opioid to the fluid infused SC. Adding hyaluronidase to the infusion (approximately 450 U/ml final concentration) allows SC administration rates of 80 to 200 cc/hr. This method allows the nurse to control the rate of infusion without mechanical pumps, simply by manually adjusting flow rate through the drip chamber. When a solution containing dextrose, with or without hyaluronidase, is administered by hypodermoclysis, fluid is drawn from the surrounding tissues to the site of injection. This effect may persist for several hours, causing unnecessary pain and decreased plasma volume. This scenario can be avoided by using a dextrose solution that contains electrolytes. The cost of hyaluronidase and occasional sensitivity reactions are the only drawbacks to this technique. More common reasons for SC needle discontinuation are given in Table 2.

SC opioids can also be administered intermittently. This is a very simple technique. However, it requires the patient or family to be adequately trained to be able to accurately draw up the opioid solution into the syringe and to inject it into the rubber gasket of the SC butterfly tubing. Finally, the most popular way of administering SC opiates is by using portable infusers. A variety of infusers, with prices ranging from $20 to $6000, are available. Ideally, a team should become familiar with a variety of portable pumps and select them according to different patient needs.

Rectal Route

The majority of published clinical experience with rectal opioids concerns short term use for acute pain. Morphine sulphate, slow-release morphine, and hydromorphone have been given rectally for pain of terminal cancer. Most patients achieve good pain control at relatively low dosages (one patient received as much as 330 mg of morphine every four hours).
Considerable individual variability exists in the absorption of rectal opiates, yet acceptable analgesia has been documented for different preparations, including aqueous solutions, suppositories, and commercially available tablets initially marketed for oral use (sustained-release and short-acting preparations).

Unfortunately, clinical data are extremely limited and there are no controlled trials on the long-term use of rectal morphine for cancer pain. Future research should focus on the relative effectiveness of the rectal route as compared to SC and other routes, on patient satisfaction and compliance, on the possibility of using this route for “rescue doses” of opioids, and on the possibility of administering other opioids besides morphine by this route.

Sublingual and Buccal Routes

There are very few reports on the clinical effects of sublingual or buccal morphine. Most of the these are single-dose studies or anecdotal experience. Whitman et al reported that 70% to 80% of 150 patients with cancer pain obtained “adequate to good pain control”. These patients received morphine sulphate tablets in a dose of 10 to 30 mg every three to four hours around the clock. Fannini treated cancer pain in 28 patients with sublingual drops of morphine hydrochloride every four hours for an average of five weeks. Future research will provide better definition of the absorption and bioavailability of various opioids given by these routes and their clinical effects and toxicity.

Transdermal Route

A number of studies have suggested that transdermal fentanyl is effective for postoperative and cancer pain. This route is exciting because of the possibility of achieving prolonged, stable blood levels of an opioid and also because it makes fentanyl, previously administered only in the hospital, newly available for the home management of cancer pain. Future research should compare clinical outcomes between the transdermal route, long-acting oral morphine preparations, and continuous SC infusions of opioids.

Inhalational Route

A number of authors have found highly variable results after using inhaled morphine or diamorphine solutions in postoperative pain and healthy volunteers. Current knowledge about the absorption and pharmacokinetics of morphine administered by the inhaled route is still quite limited. The absorption and pharmacokinetics of nebulized narcotics should be studied in more detail before reliable clinical trials can be designed.

Clinical Application of Alternative Routes

Table 3 summarizes some of the potential clinical applications of these routes in patients with cancer pain. Although there is now significant clinical experience with the use of the SC route, very limited information has been published on the clinical use of the rectal, sublingual, buccal, transdermal, and inhalational routes in patients with cancer pain. However, available pharmacokinetic data and limited clinical experience suggest specific applications for these routes in some clinical situations. All of these routes are likely to be useful for patients in whom the oral route must be bypassed because of bowel obstruction, severe emesis, or severe dysphagia. The buccal, sublingual, and inhalational routes will not be useful in patients with severe cognitive failure or comatose states, whereas the rectal route will not be useful in patients with diarrhea, colostomy, hemorrhoids, or anal fissures. The transdermal route is likely to be less useful in patients with generalized edema. Its use will be limited in patients who are medically unstable, require initial titration of the analgesic dose, need frequent dose changes, or experience breakthrough pain. The SC route is less desirable in patients with coagula-
effective in cancer pain management. On this basis, it should be considered the standard alternative systemic route against which newer systemic routes of administration should be tested.

Although controversy does exist concerning when to proceed to still more invasive means of opioid analgesia (ie, spinal, epidural, or intrathecal) clinical series argue that these more invasive routes are often appropriate when systemic administration is ineffective or poorly tolerated. A later issue of Pain: Clinical Updates will focus on these more invasive routes.

Conclusion
Current epidemiological data suggest that the number of patients who will require chronic cancer pain management is large and growing. Management of these often very ill patients in the community requires physicians, nurses, and other health care workers to transfer a large number of responsibilities to patients and their families. Safe, simple, and effective alternate routes for opioid delivery are essential for these patients. More research on this subject is badly needed—research that should take place in the home setting. Traditional assessment and management techniques may have to undergo substantial modifications so that goals of safety, efficacy, and patient preference can successfully be achieved in the patient’s home. However, these changes are mandatory because it is unlikely that the results of in-hospital research will be easily transposed to the home setting.

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References

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• Desirable Characteristics for Pain Treatment Facilities (1990)
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