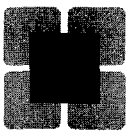

Alternate delivery methods for morphine sulfate in cancer pain

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■ New routes of opioid administration that have become available in recent years can be managed by the primary care physician or the oncologist in an attempt to improve pain control and the quality of life. Although oral morphine sulfate is the standard treatment for cancer patients with chronic pain, these novel methods of delivering morphine have enabled some patients whose pain is refractory to traditional methods of drug administration to obtain satisfactory control of their symptoms. The authors review some of these innovative methods.

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MOST CANCER PATIENTS with pain obtain adequate relief when oral morphine sulfate is administered by scheduled and individualized doses every four hours. Some patients, however, do not respond favorably to standard analgesic therapy.[1,2] In recent years, several new options have become available for treating cancer patients with pain that is refractory to standard treatment because of unacceptable pain control or adverse effects. Some patients may benefit from the addition of adjunct analgesics, neurosurgical or anesthetic procedures, or behavioral techniques in pain modification. This discussion reviews novel preparations or different routes of administration of morphine sulfate that can be managed by the primary care physician or the oncologist in an attempt to improve pain control and the quality of life (*Table 1*).

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NONPARENTERAL ROUTES OF ADMINISTRATION

Rectal suppositories

Morphine suppositories can provide an alternate form of morphine for patients who are unable to take oral or parenteral morphine.[3–5] There are many reasons why patients cannot take oral or parenteral drugs, including persistent nausea and vomiting, mental status change, obstructive head and neck or gastrointestinal tumors, poor vascular access, and coagulation problems.

In one study, six cancer patients received the same dose of oral morphine solution or rectal morphine suppositories at 10–41 mg every four hours.[3] The conversion ratio of the oral form of morphine to the rectal suppositories appeared to be a one-to-one milligram conversion. Both dosage forms provided good pain control with no significant adverse effects on respiration and no differences in the incidences of sedation or nausea.

The absorption of oral and rectal morphine preparations was evaluated in another study.[4] Ten adult cancer patients with pain were given one 10-mg dose of oral morphine sulfate solution or the morphine suppository on sequential days. Blood samples were obtained, and

the plasma levels of both morphine and one of its major metabolites, morphine-3-glucuronide, were measured. This single-dose study showed that a significantly higher plasma morphine level was observed for the rectal suppository dosage form than for the oral solution during a 4 1/2-hour period. It was concluded that the rectal administration of morphine was not affected by the first-pass metabolism of the liver to the same extent as oral morphine. The investigators did not perform a steady-state pharmacokinetic study in which multiple doses of two forms of morphine were administered.

Although the side-effect profile of the rectal suppositories was similar to oral and parenteral morphine, a unique side effect of the rectal form of morphine can be the tissue-irritating property of the drug. The rectal suppositories are available in doses of 5, 10, and 20 mg and are usually administered every four hours.

TABLE 1
NOVEL PREPARATIONS AND DIFFERENT ROUTES OF ADMINISTRATION OF OPIATES

Nonparenteral
Rectal suppositories
Sublingual
Buccal
Sustained-release preparations
Parenteral
Continuous intravenous infusion
Continuous subcutaneous infusion
Patient-controlled analgesic (PCA) systems

Sublingual administration

The sublingual route of administration of morphine sulfate also has the advantage of avoiding parenteral administration when the patient is unable to swallow the medication due to any of the conditions described above. The sublingual route of administration theoretically does not subject the drug to first-pass liver metabolism that occurs after oral ingestion and absorption from the gastrointestinal tract.

Studies of the efficacy of sublingual morphine have yielded contradictory results.[5–8] One report advocates the usefulness of morphine sulfate solution at 20 mg/mL concentration administered sublingually.[6] A tuberculin syringe was used to measure and administer the solution. The dose was administered a few drops at a time to allow maximal sublingual absorption and to minimize swallowing of the solution. A dose equivalent to the parenteral morphine sulfate dose was used initially and subsequently titrated for each individual to an analgesic effect. The authors concluded that the concentrated morphine solution allowed a smaller and more practical volume to be administered sublingually to the patients. The use of morphine sulfate solution sublingually was believed to be more desirable than the tablets because the tablets may require a longer retention time for dissolution and absorption than a morphine solution.

Sublingual absorption of opioid analgesics was studied in 10 normal volunteers.[7] The solution pH and swallowing was controlled. The subjects were trained not to swallow a 1-mL volume of solution sublingually placed for 10 minutes. The solution was then expectorated, and the concentration of drug was determined. The values for percent absorption were morphine 19%, oxycodone 15%, hydromorphone 25%, and methadone 27%. The authors concluded that these opioids do not have rapid or extensive sublingual absorption. More studies are necessary to further elucidate the absorption and pharmacokinetics of the sublingual absorption of opioid analgesics.

Buccal administration

Some investigators have shown that buccal administration is a safe and effective method of giving morphine sulfate.[9] In a well-designed prospective double-blind study of 40 patients who experienced pain after elective orthopedic surgery, buccal and intramuscular preparations of morphine produced comparable degrees of postoperative analgesia. The intramuscular preparation was shown to have a slightly higher peak plasma morphine level than the buccal administration; however, the plasma morphine levels declined more slowly after buccal administration. The slower decline in the plasma morphine levels with these buccal preparations was interpreted by the authors to be associated with an enhanced pain relief and a decreased incidence in side effects. The buccal morphine's bioavailability was 46% greater than the intramuscular morphine's bioavailability. The main side effects of the buccal preparation were dizziness, drowsiness, and a bitter taste. The adverse effects of the buccal morphine were thought to be less than those of intramuscular morphine.

In this study, the buccal preparation appeared to have reliable absorption, a slow and predictable release, and a lack of first-pass metabolism. This route of administration of morphine sulfate may be of particular value in patients unable to take oral or parenteral analgesics, but the administration of higher doses required by some cancer patients may be difficult with the dosage forms available. Clinical experience using this morphine preparation for chronic pain in cancer patients is currently lacking.

Sustained-release preparations

Approximately two-thirds of patients are satisfactorily controlled by an oral morphine dose of 30 mg or less every four hours.[1] The short duration of action of morphine necessitates a frequent and sometimes inconvenient dosage schedule of every three to four hours around the clock. When therapeutic failures with morphine therapy occur, it is often due to inadequate schedules or doses.

In treating the terminally ill cancer patient with severe chronic pain, sustained-release morphine tablets have been shown to be efficacious. The use of sustained-release morphine tablets is most valuable in a patient in whom the dosage is titrated and who is stabilized with oral immediate-release morphine approximately every four hours but has difficulty with the four-hourly regimen and the doses in the middle of the night.[1]

Converting the patient stabilized on oral immediate-release morphine to sustained-release tablet is performed by a 1 mg-to-1 mg conversion. If converted to an every 12-hour schedule, one-half of the total 24-hour dose of immediate-release morphine is administered every 12 hours. If converted to an every eight-hour schedule, one-third of the total 24-hour dose of immediate-release morphine is administered every eight hours. With either method of conversion, the dose and schedule should be adjusted to the individual needs of the patient. Occasionally, breakthrough pain occurs before the next scheduled dose of the sustained-release tablet. Approximately 25%–33% of the next scheduled sustained-release tablet dose should be administered as a "rescue dose" in the form of immediate-release morphine sulfate in order to obtain faster relief of the breakthrough pain.

Sustained-release morphine tablets have been used with success in controlled studies of cancer patients when administered every eight to 12 hours and were comparable to oral morphine sulfate administered every four hours in both efficacy and side effects.[10–13] Although most patients will have adequate pain control with 12-hour dosing intervals, some patients may require eight-hour intervals. Currently, the sustained-release preparations are available in 60-mg tablets and administered orally approximately every eight to 12 hours.

PARENTERAL ROUTES OF ADMINISTRATION

Continuous intravenous infusion

Continuous intravenous infusion of morphine sulfate may be useful in the treatment of refractory pain.[14–17] While morphine sulfate is the most commonly used narcotic administered by this route, methadone, meperidine, and hydromorphone have also been given in this manner. When administered as a continuous intravenous infusion, methadone may cause dosing problems because of its relatively long half-life, and chronically administered meperidine may have increased adverse effects, particularly of the central nervous system because of the accumulation of toxic metabolites.[18]

The doses are generally titrated to the needs of the patient. The mean starting dose expressed in morphine equivalents in one study of cancer patients with chronic pain was 17 mg/h; subsequently, the mean maximum infusion rate was 69 mg/h.[16] Commonly used doses of intravenously infused morphine sulfate have ranged from 1–100 mg/h in adults; however, rates as high as 250 mg/h are occasionally required. The patient's vital signs and mental status should be carefully monitored during the dose escalation, although it has been shown that careful titration of the dose does not significantly compromise the pulmonary status of most patients. Rate-controlled external pumps and implantable infusion pumps are now being studied for intravenous infusion of narcotics in ambulatory patients.[17]

A practical problem associated with continuous intravenous infusion of morphine sulfate is the need for sustained venous access. In the ambulatory setting, a central venous line is most commonly established with a subcutaneous venous access device. The most common side effects seen with continuous infusion morphine therapy are similar to those that occur with other routes of morphine administration: somnolence, hallucinations, constipation, respiratory depression, and confusion. Marked somnolence and bradypnea is usually the cause for dose reduction.[17]

Continuous subcutaneous infusion

The advantage of continuous subcutaneous infusion of morphine is that it does not require a sustained venous access.[19,20] A rate-controlled infusion pump is connected to a small-gauge butterfly needle, which the patient or family member is trained to insert subcutaneously. The site of the needle is changed every 24–48 hours usually by a family member at home. Because of an increased incidence of tissue irritation, it is not advisable to give meperidine by the subcutaneous route.

The method of continuous subcutaneous infusion of opiates was studied in 15 patients with pain from cancer.[19] The drugs used were hydromorphone, levorphanol, methadone, and most frequently, morphine. Although the investigators emphasized that most patients with cancer pain are adequately controlled with oral

analgesics, the subcutaneous infusion of opiates was effective and safe. The most frequent adverse effect was local irritation at the site of the subcutaneous needle, especially when the volume required was greater than 1 mL per hour.

Administration by subcutaneous infusion offers the same advantages as continuous intravenous infusion of morphine. However, subcutaneous administration is contraindicated in patients with coagulation problems because of the potential development of hematomas from the subcutaneous needle. There is little data on the pharmacokinetics of subcutaneous morphine; however, judging by the clinical analgesic effects, the drug appears to be well absorbed.

Patient-controlled analgesic systems

Patient-controlled analgesia (PCA) is a new technique for the administration of injectable narcotics, particularly morphine sulfate. The PCA administration system is designed to allow the patient to self-administer optimal amounts of medication. The dosages and time intervals are preset into a microprocessor-controlled infusion pump. When the patient experiences pain, a button is depressed by the patient and a dose of the medication is administered intravenously or subcutaneously. Along with the self-administered dose of medication, some devices also deliver a continuous infusion of narcotic as a basal rate. If the patient should depress the button before the preset time interval has elapsed, no extra drug is administered.

Published studies regarding PCA mostly involving postoperative patients have shown that the technique offers good analgesic efficiency with minimal sedation and respiratory depression. In a review, more than 40 studies were examined for efficacy of PCA; however, few studies compared the effectiveness of PCA with conventional analgesia.[21] Particularly lacking are studies of the use of PCA for treatment of chronic pain in cancer patients.

A recent study compared PCA with continuous-infusion morphine for the treatment of oral mucositis pain in patients receiving high-dose chemotherapy and bone-marrow transplantation.[22] The ratings for pain, alertness, and general mood did not differ between the two treatment groups. The group of patients using PCA achieved good pain control with significantly less morphine and nausea than the group using continuous-infusion morphine. It will be particularly interesting to evaluate the new portable PCA devices for subcutaneous opioid analgesic administration in ambulatory cancer patients with refractory chronic pain.

CONCLUSION

Although most patients with cancer obtain pain relief with standard oral medications throughout most of the clinical course, some pain is refractory to these medications and some patients experience adverse effects that compromise their quality of life. Because of recent development of new devices and delivery systems for opioid analgesics, a number of alternatives are available for treatment of cancer patients with inadequate pain management. Much more study of the efficacy and safety of each of these methods is needed to determine where each of these types of therapy belongs in the routine treatment of cancer patients with chronic pain.

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