



Several routes of opioid administration are used to control cancer-related pain, and each has individual pharmacokinetic actions.

Charles Blomfield. *White Terraces, Rotomahana*, c1897. Oil on canvas, 405 × 553 mm. Courtesy of Auckland Art Gallery Toi o Tamaki. Gift of Dagmar Graham in memory of Ernest Robert Blomfield Graham, 1995.

Routes of Opioid Analgesic Therapy in the Management of Cancer Pain

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Background: *The availability of various routes of administration of opioid analgesics can be confusing when determining an appropriate, efficacious, and cost-effective regimen to manage cancer pain.*

Methods: *The indications, contraindications, and pharmacokinetic properties of oral, intravenous, subcutaneous, transdermal, transmucosal, rectal, and perispinal routes of opioid administration are reviewed.*

Results: *To determine the most efficacious, cost-effective, and user-friendly option to manage cancer pain, several factors must be considered: the ability of the patient to use a specific type of delivery system, the efficacy of that system to deliver acceptable analgesia, the ease of use for the patient and family, the potential or actual complications associated with that system, and the cost.*

Conclusions: *Administering opioids to manage cancer pain requires knowledge of potency relative to morphine and bioavailability of the route chosen. Changes in the route, dosage, or opioid used should be accompanied with close patient follow-up.*

Introduction

The variety of options for the delivery of opioids in the management of cancer pain can be confusing. In

some instances, there are clear indications for using one preparation or delivery system over another. These indications may take into consideration the ability of the patient to use a specific type of delivery system, the efficacy of that system to deliver acceptable analgesia, the ease of use by the patient and his or her family, and the potential or actual complications associated with that system. Cost is another important consideration for patients who must purchase their own medications. Increasingly, patients in managed care systems may be limited in the choice of analgesics by their managed care organization, which may restrict access to certain medications based on their cost.

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Table 1. — Bioavailability of Opioids by Route of Administration

Route	Bioavailability
Oral	33% (morphine) 60%-87% (oxycodone)
Intravenous	100% (all opioids)
Subcutaneous	80% (hydromorphone)
Transdermal	90% (fentanyl)
Transmucosal	30%-60% (morphine, fentanyl)
Rectal	30%-40% (morphine)

This article addresses the variety of delivery options for opioids available for the management of cancer pain, with emphasis on the indications, contraindications, and pharmacokinetic differences (eg, time to peak effect and bioavailability) among systems (Tables 1-3) and relative cost of the various systems (Table 4). The systems discussed are oral, intravenous, subcutaneous, transdermal, rectal, and transmucosal. Because of space considerations, the perispinal opioid systems will be discussed only briefly in this article. This information is important in assisting the physician choose the most efficacious, cost-effective, and user-friendly option for each patient with cancer pain.

All of the opioid analgesics discussed in this article are potent mu-agonists. By binding to the mu-receptors, they exert analgesia and at the same time affect respiration and gastrointestinal motility. Although the mixed agonist-antagonist opioids (eg, butorphanol) are sometimes prescribed for chronic pain, they have no place in the treatment of cancer pain because of their antagonistic effects at the mu receptor. Likewise, "partial" mu-agonists (eg, buprenorphine) have a "ceiling effect" of analgesia; dose escalation above a certain point does not enhance analgesia. These agents also have no role in the treatment of cancer pain. The weak mu-agonists, such as codeine, hydrocodone, and propoxyphene, are usually found in combination with aspirin or acetaminophen. Taken in large daily doses, the aspirin or acetaminophen compound becomes the limiting factor due to potential hepatic toxicity. Therefore, this article does not discuss the mixed agonist-antagonist, partial agonist, or weak mu-agonist opioid analgesics. Discussion will be limited to the potent mu-agonists opioids (eg, morphine, methadone, oxycodone, hydromorphone, fentanyl, and sufentanil).

The Oral Route

The oral route is the most common, least invasive, and easiest route for opioid administration for most patients with cancer pain. In all patients who can take oral medications, this route should be considered first.¹

There are no major complications (other than opioid side effects) associated with the oral route in patients who can take oral medications. Certain patients, because of oesophageal motility problems or gastrointestinal obstruction (eg, head and neck or oesophageal cancer), may not be able to tolerate oral medications. In these cases, an alternative form of analgesia must be used. The main problem with the oral route is first-pass biotransformation of opioids in the liver. All opioids given orally are absorbed via the gastric and duodenal mucosa and then transported to the liver via the portal venous system. In the liver, these medications undergo "first-pass metabolism" before entering the systemic circulation. This has a major impact on the systemic plasma concentrations of drugs.

Bioavailability is defined as the percentage of administered medication that reaches the systemic circulation (Table 1). First-pass metabolism decreases the bioavailability of morphine to 30% to 40%,^{2(p2330)} methadone to 50%,^{2(p2546)} and oxycodone to 60% to 87%.^{2(p2344)} of the total administered dose. For example, the dose of an opioid given orally to a patient with cancer pain must be three times the intravenous or intramuscular dose of morphine and twice the parenteral dose of methadone. Oxycodone, while roughly equipotent to morphine if given parenterally, appears to be approximately twice as potent as morphine when given orally because of less first-pass metabolism. Therefore, both the bioavailability of a drug and its potency relative to morphine must be considered when calculating equivalent opioid doses (Table 2).

Morphine, the most commonly used medication in the world to treat cancer pain, has a terminal elimination plasma half-life of 3.1 hours.^{2(p2330)} To provide

Table 2. — Relative Potencies of Opioid Analgesics Compared to Morphine*

Drug	Parenteral Relative Potency	Oral Relative Potency
Morphine	1	1
Hydromorphone	5	5
Meperidine	0.2	0.2
Methadone	1	2
Codeine	0.16	0.16
Oxycodone	1	2
Fentanyl	100	200

* The oral relative potency is the product of the parenteral potency compared with morphine multiplied by the oral bioavailability of the drug compared with morphine. For parenteral administration, the bioavailability of all drugs = 1.0. The oral bioavailability of morphine = 0.3. Thus, oral oxycodone is approximately twice as potent as oral morphine because its bioavailability is twice that of oral morphine.

longer-lasting analgesia, several preparations have become available on the North American market in recent years that provide for a slow release of morphine. Some of these long-acting preparations use a hydroxyethyl cellulose and hydroxypropyl methylcellulose matrix to surround the active drug. The cellulose then slowly dissolves in the stomach and small intestine, resulting in a sustained release of the active drug. Bioavailability of these slow-release preparations is the same as that of immediate-release preparations (ie, 0.33), but time to peak plasma drug concentrations (T_{max}) is longer, and peak plasma concentrations (C_{max}) is decreased.^{2(p2330)} Examples of slow-release opioid preparations are MS Contin (morphine; Purdue Pharma, Norwalk, Conn), available in 15, 30, 60, 100, and 200 mg tablets, and OxyContin (oxycodone; Purdue Pharma), available in 10, 20, 40, and 80 mg tablets. MS Contin and OxyContin are recommended by the manufacturer to be administered every 12 hours. Clinicians occasionally use an 8-hour schedule, if necessary to provide adequate analgesia. Kadian (morphine; AstraZeneca, Wilmington, Del),

available in 20, 50, 100 mg tablets, is a morphine pellet coated with a polymer^{2(p3166)} and should be administered once every 24 hours.

A long-acting opioid preparation given on a scheduled ("around-the-clock") basis is preferred to provide analgesia for cancer patients.¹ If additional analgesia is needed for "breakthrough" pain, doses of a fast-onset, short-acting opioid preparation should be available to the patient. Immediate-release oral opioid preparations usually require approximately 30 minutes to onset of analgesic action when taken on an empty stomach. When taken on a full stomach, the onset of action of immediate-release opioids is delayed. In contrast, the onset of action of slow-release opioids may not be delayed by food present in the stomach.

Commonly available immediate-release preparations are MSIR (Purdue Pharma; immediate-release morphine sulphate) and OxyIR (Purdue Pharma; immediate-release oxycodone). These preparations are simply the parent compound. MSIR is available in capsule form in doses of 15 and 30 mg. Morphine sulphate solution is also available in 10 mg/5 mL and 20 mg/5 mL (MSIR oral solution) and 20 mg/mL (MSIR oral solution concentrate). OxyIR is available in 5-mg capsules. OxyFast (Purdue Pharma) is a liquid formulation of oxycodone in 20 mg/mL concentration. OxyIR contains the same active ingredient (oxycodone 5 mg) in the same dose as Percocet and Percodan tablets (Endo Laboratories, Wilmington, Del). In addition to oxycodone, Percocet contains acetaminophen 325 mg and Percodan contains aspirin 325 mg.

Methadone possesses a terminal plasma half-life of approximately 24 hours and an oral bioavailability of 50%. It is often used as an oral analgesic in the treatment of cancer pain. When given intravenously, methadone is equipotent to morphine. However, because of lower first-pass metabolism than morphine, it is approximately

Table 3. — Relative Advantages and Disadvantages of Various Routes of Opioid Administration

Route	Advantages	Disadvantages
Oral	Easy to administer (self or family) Fewest complications Well tolerated Inexpensive Slow-release formulations available	Lowest bioavailability
Intravenous	Highest bioavailability Rapid dose titration Not limited by infusate volumes	High cost Requires intravenous access Risk of infection Requires skilled nursing support
Subcutaneous	High bioavailability Intravenous access not required Rapid dose titration	High cost Infusate volume limited to 1-4 mL/hr (requires concentrated opioid solution) Requires skilled nursing support Induration may occur at site
Transdermal	Easy to administer (self or family) Few complications Long duration of action (72 hrs)	May cost more than oral Cannot perform rapid dose titration Some patients cannot tolerate patch Side effects not quickly reversible
Transmucosal	Higher bioavailability than oral Fast absorption	Higher cost than oral Only fentanyl available No long-acting preparation
Rectal/Ostial	Possibly higher bioavailability than oral Available for patients who cannot take oral medications Can use long-acting oral preparations Low cost Can be self- or family-administered	Less attractive than oral route for some individuals/cultures

Adapted from Jacox et al.²⁷

twice as potent when given orally (bioavailability = 0.5 to 0.6). Methadone is available as a tablet (5 and 10 mg), oral solution (5 mg/5 mL and 10 mg/5 mL), oral concentrate (10 mg/mL), powder, and diskette (dispersible 40 mg tablet). The latter is indicated for use in opioid addiction treatment programs; the diskette is dissolved in water or juice. However, this method of administration could be used for control of cancer pain. Despite a long terminal plasma half-life, methadone, when used to control cancer pain, is frequently administered in divided doses, 2 to 3 times per day, although theoretically once-daily doses should be adequate.

Hydromorphone (Dilaudid, Knoll Laboratories, Mount Olive, NJ) is a potent mu-agonist, approximately 5 times more potent than morphine when given intravenously. It has a terminal plasma half-life of 2.6 hours. It is approximately 50% bioavailable when given orally and is available in tablets (2, 4, and 8 mg), in oral solution (5 mg/5 mL), and as a rectal suppository (3 mg). There is no clear advantage to using hydromorphone over morphine when the medications are given in equipotent doses orally. Anecdotally, some patients may have less gastrointestinal intolerance to one opioid than another.

Many patients will develop tolerance to most of the undesirable side effects of opioids (such as nausea/vomiting or sedation) over a period of several days; therefore, a medication should not be labelled "intolerable" until a reasonable trial has been undertaken.

The Intravenous Route

While most patients can be adequately managed using the oral opioids, a small percentage require alternative routes, either because they are unable to swallow due to the site of their cancer or because they are receiving end-of-life care, when an inability to take oral medications may arise. The intravenous route of administration is available for those patients whose pain cannot be controlled by a less invasive route. The major disadvantage of this route is that it requires continuous intravenous access, such as a Port-a-Cath (Pharmacia, St Paul, Minn) or other types of in-dwelling central or peripheral catheters. Any in-dwelling intravenous catheter can serve as an entry

port for infection and thus requires skilled nursing attention if the patient is unable to care for the catheter access. Significant costs are incurred when placing a permanent intravenous access, preparing the opioid solution for injection by the pharmacist, and administering the infusion via an external pump. For outpatients, having an intravenous opioid infusion for pain control may require outpatient nursing support, which also may incur significant costs. For these reasons, the intravenous route is used only when less invasive routes are not appropriate.

Of all the opioids available in intravenous solution, the most commonly used in North America for treating cancer pain are morphine, hydromorphone, fentanyl, and sufentanil. Meperidine, a semisynthetic opioid, is not commonly used for long-term intravenous infusion because its first-order metabolite, normeperidine, can accumulate in patients with decreased renal function and can cause central nervous system toxicity, including seizures.³

Morphine is available for administration as an intravenous solution in several concentrations. Morphine sulphate USP (Astra Merck, Westborough, Mass) is available in 1 mg/mL, 2 mg/mL, and 25 mg/mL concentra-

Table 4. — Current Relative Cost to the Pharmacist for Medications Only*

Route	Bioavailability	One day (\$ US)	30 days (\$ US)
Oral MS Contin @ 120 mg twice daily	33%	18.16	425.66
Intravenous** Morphine (1 mg/mL) @ 3.3 mg/hr	100%	17.08	381.96
Subcutaneous** Hydromorphone (1 mg/mL) @ 0.9 mg/hr	80%	24.22	726.62
Rectal MS Contin @ 120 mg twice daily	33%	18.16	425.66
Transdermal Duragesic fentanyl @ 50 µg/hr	90%	8.16	204.21

* Average wholesale prices are based on approximately equivalent doses. The equivalent dose of slow-release morphine 120 mg twice daily is used for comparison.

** Intravenous and subcutaneous infusions involve additional costs for intravenous tubing, needles, dressings, insertion of the in-dwelling catheter or Port-a-Cath (for the intravenous route), and home nursing care. These additional costs will likely be much more than the costs of the drugs alone.

Prices were kindly supplied by Michael Schuh, RPh, of Mayo Clinic Pharmacy, Jacksonville, Fla.

tions for intravenous infusion. Infumorph 200 and 500 (Elkins-Sinn, Cherry Hill, NJ) are available in dosages of 10 mg/mL and 20 mg/mL, respectively, for intrathecal, epidural, or intravenous infusion. Morphine sulphate (Tubex, Wyeth-Ayerst Laboratories, Philadelphia, Pa) is available in several dosages ranging from 2 mg/mL to 15 mg/mL. Since this formulation may contain a preservative, it is not recommended for continuous intravenous, epidural, or intrathecal infusion. Morphine solutions for injection can also be prepared from morphine tablets, which are crushed and dissolved in sterile saline, then sterilized by passing the solution through a bacterial filter. The concentrations can be made to order, with the maximum concentrations of 50 to 55 mg/mL, limited by the solubility of morphine.

Hydromorphone is available as a solution for intravenous injection in 1, 2, and 4 mg/mL. Dilaudid HP (Knoll Laboratories) is available in 10 mg/mL concentration for intravenous, epidural, or intrathecal infusion. The morphine equivalent potency of this solution would be approximately 50 mg/mL.

Fentanyl and sufentanil are both highly lipid soluble and thus highly potent synthetic opioids. Their main use has been in anesthesia; however, they have been used extensively in intravenous, epidural, and intrathecal continuous infusions to manage cancer pain in patients who are tolerant to opioids, such as morphine. Fentanyl and sufentanil (Janssen Pharmaceutica, Inc, Titusville, NJ) are both available in 50 µg/mL concentrations. Fentanyl is approximately 100 times more potent than morphine, and sufentanil is approximately 1,000 times more potent. The main drawback to their use in the practice of oncology is their high cost compared with the cost of morphine. Therefore, these analgesics are rarely used for intravenous infusions in cancer patients but are commonly used for epidural, intrathecal, or subcutaneous infusions (see below), all of which require a smaller volume of injectate per unit of time than for intravenous infusions. Intravenous opioid infusions can be given as continuous infusions, or they can be used in conjunction with a patient-controlled analgesia (PCA) device, which provides continuous infusion plus on-demand boluses. Both intravenous and subcutaneous PCA opioids have been shown to be effective in both inpatients and outpatients.^{4,6} However, confused patients may not be the best candidates for PCA use.⁷

The Subcutaneous Route

For patients requiring parenteral opioids who do not have in-dwelling intravenous access, the subcutaneous route can be used.⁸ This simple method of par-

enteral administration involves inserting a 25- or 27-gauge butterfly needle and attaching the tubing to an infusion pump. An area on the chest, abdomen, upper arms, or thighs is shaved and prepared with povidone-iodine. The butterfly needle is held in place by a bandage over the plastic butterfly wings. A clear plastic occlusive dressing is then applied to cover the needle, and a loop of tubing is secured with adhesive tape. The injection site should be changed weekly or as needed. The limiting factor is the volume of fluid that can be injected per hour. Infusion rates of 2 to 4 mL per hour have been found to be satisfactory without causing pain at the infusion site.⁹ Therefore, concentrated solutions of morphine or hydromorphone are commonly used.

The subcutaneous route is usually used in conjunction with a PCA device such as the CADD pump (Pharmacia Deltec Inc, St Paul, Minn), which provides the patient with better control over the analgesia than does a continuous infusion alone. The bioavailability of hydromorphone using a PCA device has been shown to be approximately 80% in cancer patients when given via the subcutaneous route.¹⁰ Steady-state plasma hydromorphone concentrations were reached within 24 hours in this study. Conceivably, fentanyl or sufentanil could be used, although the cost would be higher than that of morphine or hydromorphone. There is a high degree of effectiveness in providing adequate analgesia to cancer patients with a low rate of skin infections (1 of 117 patients in one study) using subcutaneous PCA opioids.¹¹ The main advantages of subcutaneous over intravenous PCA is that there is no need for vascular access, changing sites can be easily accomplished, and problems associated with in-dwelling intravenous catheters are avoided.

The Transdermal Route

For patients unable to take oral medications, the transdermal route is a noninvasive option of maintaining continuous plasma concentrations of opioids. At present, fentanyl (Duragesic patch, Janssen Pharmaceutica) is the only medication available in this form. This delivery system, which is similar for other transdermal delivery systems (eg, nitroglycerine), consists of a reservoir of fentanyl and alcohol that contains a 3-day supply of fentanyl.¹² The drug reservoir is separated from the skin by a permeable membrane that controls the rate of release of fentanyl from the reservoir. A fentanyl-saturated adhesive layer holds the system in place and administers a "bolus" of fentanyl after the patch is applied. The patch releases fentanyl at a constant rate until the reservoir is depleted. Alcohol (0.1 mL/10 cm²) is used in the patch to increase the permeability of the skin to fentanyl. Only trace amounts of alcohol are

actually absorbed systemically. Upon initial application of the patch, a subcutaneous "depot" is formed as fentanyl saturates the subcutaneous fat beneath the patch. After approximately 12 hours, steady-state plasma fentanyl concentrations are reached, which are maintained for about 72 hours. Fentanyl patches are currently available in 25, 50, 75, and 100 µg/hr dosages. Multiple patches may be placed if higher doses are needed. The bioavailability of transdermal fentanyl has been calculated in one study to be approximately 90%.¹³ Transdermal fentanyl has become an effective tool in the management of cancer pain.

Several pharmacokinetic properties concerning transdermal fentanyl are of interest to the clinician. One is that drug permeation through human skin, expressed as a coefficient of variation, can vary from 46% to 66% among individuals.¹⁴ In any individual patient, drug penetration can vary among skin regions by 20% to 40%. Nonetheless, permeability coefficients are adequate through diverse skin sites such as the abdomen, chest, arm, and thigh. A 100-µg/hr patch would initially contain 10 mg of fentanyl. Over a 24-hour period, approximately 3.4 mg is absorbed systemically, while the rest remains in the patch. Because a depot of fentanyl is formed in the subcutaneous fat from which fentanyl is absorbed into the systemic circulation, an estimated 1 mg of fentanyl remains in the skin depot after removal of a 100-µg/hr fentanyl patch which has been in place for 24 hours.¹³ Vigorous exercise and elevation of body temperature secondary to fever or bathing will increase blood flow to the skin and increase drug diffusion into the systemic circulation.¹⁵ Although the terminal elimination half-life of an intravenous bolus of fentanyl is 2 to 4 hours, the apparent half-life of fentanyl after removal of a transdermal system is 14 to 25 hours due to the formation of a subcutaneous depot.¹² These factors have two implications in clinical care: (1) because of the slow depot formation and slow rise in plasma concentrations, this system is not suitable for rapid titration of pain, and (2) because of the prolonged elimination after removal of a system, the opioid side-effects will take many hours to resolve and may require frequent doses of naloxone if the side effects are severe enough to require treatment. Thus, the transdermal fentanyl system is best suited for patients with stable pain in whom the 24-hour opioid requirement has already been determined.

Adverse effects of the fentanyl patch are rare and usually are easily treated. Dermatological reactions characterized as transient and mild — typically skin occlusion and local irritation — rather than contact dermatitis have been reported.¹² Rotating skin sites is recommended to avoid these problems. Typical opioid side effects, eg, nausea/vomiting, constipation, somno-

lence, confusion, and respiratory depression, have all been reported, although all of these except constipation are rare in opioid-tolerant patients. In general, this delivery system is well tolerated by cancer patients with relatively constant pain who are on stable doses of opioids. Some sort of "breakthrough" pain coverage is still advised (eg, immediate-release oral morphine). In patients unable to use the oral route, the transmucosal or rectal route is available for "breakthrough" administration of fast-acting opioids.

The Transmucosal/Sublingual Routes

The sublingual administration of opioids is particularly beneficial in the patient with cancer who is unable to tolerate oral administration because of nausea/vomiting or dysphagia. It may also be attractive in patients who cannot receive parenteral opioids because of lack of venous access, emaciation, or coagulation defects.¹⁶ Furthermore, because sublingual venous drainage is systemic rather than portal, hepatic first-pass elimination can be avoided. The sublingual route also offers the potential for more rapid absorption and onset of action relative to the oral route. In general, the higher the pH of the oral cavity, the better the absorption of opioids. Lipophilic drugs are better absorbed than are hydrophilic drugs, which explains why the absorption of methadone (35%), fentanyl (51%), and buprenorphine (56%) is greater than absorption of morphine (22%).

A major advantage of sublingual drug administration is its simplicity: it requires little expertise, preparation, or supervision. The side effects are limited to a bitter taste and a burning sensation. Because of its good and rapid absorption, along with its fewer side effects, fentanyl has been the most commonly used opioid via the sublingual route in the United States. Actiq (Abbott Laboratories, Abbott Park, Ill), an oral transmucosal fentanyl preparation, has recently been marketed for treatment of breakthrough cancer pain.¹⁷ It is available in 200, 400, 600, 800, 1,200, and 1,600 µg doses. Both the plasma fentanyl concentration and bioavailability of fentanyl will vary depending on the fraction of the dose absorbed through the oral mucosa and the fraction swallowed. Approximately 25% of the total dose is rapidly absorbed from the buccal mucosa and becomes systemically available. The remaining 75% is swallowed, is slowly absorbed from the stomach, and then undergoes first-pass metabolism in the liver, with a bioavailability of 33%. Thus, the overall observed bioavailability of transmucosal fentanyl is approximately 50% of the total dose. Median time to reach maximum plasma concentration (C_{max}) varied from 20 to 40 minutes following a standardized consumption time of

15 minutes. There is limited clinical experience with this product at the present time. One drawback to widespread use may be its cost: average wholesale price per unit ranges from \$7 for the 200- μ g dose to \$21 for the 1,600- μ g dose. Because this dosage is not available in a sustained-release preparation, it is indicated only for breakthrough pain. Transmucosal fentanyl may become a very useful tool in the management of breakthrough pain in cancer patients who are unable to swallow tablets or capsules.

The Rectal Route

This route may be a simple alternative when the oral route is not possible because of vomiting, obstruction, or altered consciousness. Its principal advantage is that it is independent of gastrointestinal tract motility and rate of gastric emptying.¹⁸ This is of considerable importance with the opioid analgesics whose propensity for slowing gastric emptying and ability to induce nausea and vomiting are well known. In addition, in patients who have an ostomy, opioids may be administered directly into the ostomy by the patient, nurse, or family member.

The rectal route also has several disadvantages. There may be a great deal of variation among individuals regarding the necessary dose. Normally, drugs absorbed via the inferior and middle rectal veins bypass the portal system and empty into the vena cava. Thus, for the portion of drug absorbed into these veins, first-pass metabolism is avoided. The drugs absorbed via the superior rectal veins, however, are transported to the liver via the portal system. How much of the rectum is drained by these three veins is highly variable. Titration and individualization of doses are therefore necessary. Absorption may be delayed or limited by the small surface area of the rectum. Dissolution of tablets or capsules may be slowed because of the small amount of fluid available in the rectum. Absorption may be interrupted by defecation. Constipation may prevent contact of drug with rectal mucosa and cause subsequent absorption into feces. All these factors may affect bioavailability. There are a few contraindications to using this route. The rectal route should not be used if the patient finds it distasteful or if the patient has painful anal conditions such as fissures or inflamed hemorrhoids.

The most suitable opioid form for the rectal route is the suppository, although if necessary, any tablet of any opioid that is used for oral administration can be used rectally. Most commonly available opioid analgesics in the suppository form in the United States are morphine, hydromorphone, and oxymorphone. However, other

opioids (eg, oxycodone, codeine, and meperidine) are readily absorbed rectally. Hydromorphone is available in 3-mg suppositories, morphine in 5, 10, 20, and 30 mg suppositories, and oxymorphone in 5-mg suppositories.¹⁹ Rectally, 30 mg of morphine = 7.5 mg of hydromorphone = 10 mg of oxymorphone. One study of cancer pain control using unmodified MS Contin via the rectal route showed that the rectal dose required was the same as the oral dose to provide equivalent analgesia.²⁰ Therefore, the usual recommendation for initial doses of morphine and most other opioids given rectally is the same dose as that which is given orally. The dose can then be titrated to optimal analgesia. For increased pain with tumor progression, increases in opioid dose must be calculated in relation to the current dose. The usual recommendation for unrelieved pain is a minimum of a 25% increase in dose. When pain is severe, doses may be increased by 50% to 100%. The principle of careful titration for each patient should be followed whenever route, dose, or opioid is changed, as dose-equivalency tables and published values for bioavailability for various routes are only approximations of what may occur in an individual patient.

The Perispinal Route

The majority of chronic pain patients can be adequately controlled by the administration of opioids via one of the routes discussed above. However, a small number of patients may still fail to obtain adequate analgesia despite large systemic opioid doses, or they may suffer from uncontrollable side effects such as nausea, vomiting, or oversedation. These patients may be candidates for the administration of opioids, local anesthetics, and/or alpha-adrenergic agonists (eg, clonidine) via the perispinal (epidural or intrathecal) route.

The goal of perispinal opioid therapy is to place a small dose of an opioid and/or local anesthetic close to the spinal opioid receptors located in the dorsal horn of the spinal cord to enhance analgesia and reduce systemic side effects by decreasing the total daily opioid dose. This route has been used in cancer patients in the past but has been extended to treat refractory nonmalignant chronic pain.²¹ Use of this route to deliver opioids requires placing an in-dwelling catheter into the epidural or intrathecal space and using an external or implantable infusion pump to deliver the medications.

Contraindications to perispinal opioids include patients with unreasonable goals and expectations, psychiatric disorders, or personality traits that could interfere with successful treatment, a history of addictive or drug-seeking behavior, and any contraindications for epidural or spinal catheter placement such as

coagulopathy, infection at the site of catheter insertion, or sepsis.²²

The various perispinal (neuraxial) approaches for opioid delivery include epidural bolus, continuous epidural infusion, intrathecal injection, and continuous intrathecal infusion. Deciding between epidural vs intrathecal placement or external vs implantable pumps to deliver the opioid is based on multiple factors including duration of therapy, type and location of the pain, disease extent and central nervous system involvement, opioid requirement, and individual preference. For instance, since the daily epidural opioid requirement is approximately 10 times that of intrathecal administration,²³ an expected duration of therapy exceeding 6 months may favor an intrathecal catheter placement to minimize refills of the pump or drug reservoir. Intrathecal opioid administration has the advantage of allowing a higher concentration of drug to be localized at the receptor site while minimizing systemic absorption, thus possibly decreasing drug-related side effects. This would be useful in opioid-resistant pain states (eg, neuropathic pain) in which high doses of opioids are often used, although there is no evidence that perispinal opioids are more efficacious than systemic opioids in treating neuropathic oncologic pain (Tables 5-6).

Of all the known opioids, morphine remains the drug of choice for the perispinal route. Compared with

Table 5. — Potential Advantages of Epidural and Intrathecal Placement

Epidural	<p>Reduced risk of post-dural puncture headache and/or chronic cerebrospinal fluid leak compared with the intrathecal route.</p> <p>Dura acts as barrier to infection; if infection occurs, it is more likely to be limited to epidural abscess (as opposed to meningitis).</p> <p>Permits greater flexibility in selection of site; a local anesthetic may be added to provide a measure of segmental analgesia.</p> <p>Margin of safety may be increased in the case of accidental overdose.</p>
Intrathecal	<p>Less risk of catheter obstruction from epidural fibrosis or metastases.</p> <p>Less likelihood of pain on injection because no intrathecal fibrosis occurs around the catheter.</p> <p>Analgesia is often more intense, rapid in onset, and longer in duration.</p> <p>Lower doses (and volume) of opioid are required to produce analgesia (about 1:10 in the case of morphine); when long-term use is likely, doses associated with predominantly spinal (as opposed to systemic) effects can be used longer.</p>

Table 6. — Comparison of Continuous Infusion and Intermittent Bolus Administration

<p>Potential Advantages of Continuous Infusion</p> <ul style="list-style-type: none"> More consistent level of analgesia Reduced dosage requirements Reduced nursing care Reduced handling of catheter/infection Potential for addition of patient-controlled analgesia
<p>Potential Disadvantages of Continuous Infusion</p> <ul style="list-style-type: none"> Expense of infusion devices and opioid solutions Availability of trained personnel to service pumps and monitor care (ie, home health care nursing agencies) Potential for pump malfunction Potential for errors in prescribing and refilling infusion device

other opioids, morphine has a relatively low lipid solubility. Thus, it has a slow onset of action (1 to 2 hours) and a long duration of analgesia (10 to 12 hours) when given via intermittent bolus. The starting dose can be calculated by dividing the prior 24-hour oral morphine dose by 3 to obtain the equipotent intravenous morphine dose. The 24-hour epidural morphine dose is approximately 0.25 to 0.30 of the intravenous dose, and the intrathecal dose is approximately 0.10 the epidural dose (Table 7).

There have been occasional reports of withdrawal symptoms in patients after converting large systemic opioid doses to intrathecal infusions.²³ This is not generally a problem when converting systemic opioids to epidural infusions due to systemic uptake of some of the epidural opioid. This problem can be avoided if careful conversion and titration are performed. One half of the initial systemic opioid dose is converted and given via perispinal infusion therapy. The other half is given parenterally and then diminished by 10% to 20% per day. The perispinal infusion can then be gradually increased by 10% to 20% per day as required.

Clonidine, an alpha-adrenergic agonist that acts at the dorsal horn of the spinal cord to produce analgesia (as well as orthostatic hypotension in higher doses), has been used in cancer patients in combination with epidural (or intrathecal) morphine infusions. This drug has been released in the United States for perispinal use within the last 2 years, so clinical experience with this drug in this setting is limited. Its role will probably be one of an adjunct to perispinal morphine. When it is given in larger doses, it usually results in orthostatic hypotension, which limits its usefulness in ambulatory patients. There is some evidence to suggest that neuropathic pain may be somewhat more responsive to the combination of clonidine/morphine than to morphine alone.

Table 7. — Calculation of Narcotic Dose for Neuraxial Trial and/or Treatment Starting Dose

Step 1:	24-hr Oral Morphine Dose (or Other Opioid Equianalgesic Dose)	÷	3	=	24-hr Parenteral Morphine Dose
Step 2:	24-hr Parenteral Morphine Dose*	÷	3 (or 4)	=	24-hr Epidural Morphine Dose
Step 3:	24-hr Epidural Morphine Dose	÷	10	=	24-hr Intrathecal Morphine Dose
* Give one-half equianalgesic dose secondary to incomplete cross-tolerance among opioids.					

The complications and side effects associated with the perispinal approach can generally be divided into three categories: procedural and surgical complications, system malfunction, and pharmacologic side effects (eg, respiratory depression and oversedation).

Surgical complications include infection²⁴ and/or bleeding at various sites (meningeal, epidural, pump pocket, pump reservoir, and/or incisional sites), seroma, cerebrospinal fluid hygroma, and postdural puncture headache. The complications related to a system malfunction include kinking, obstruction, disconnection, tearing or migration of the catheter. The incidence rate can be as high as 10% to 40%.²⁵ Pharmacologic overdoses can be avoided with accurate drug conversions and calculations (Table 7). Vigilance and meticulous attention to details will help to prevent catastrophic pump filling errors. In general, with the exception of constipation, side effects of perispinal opioids in patients already tolerant to opioids are rare.

Other pharmacologic concerns include the development of tolerance and hyperalgesia. The former can be explained by a decrease in the sensitivity of the opioid receptors. This problem should eventually reach a plateau and can be managed with a "drug holiday" if it remains problematic.²² A "drug holiday" entails interrupting therapy for 2 to 3 weeks to re-sensitize the opioid receptors. During that time, oral opioids or spinal infusions of local anaesthetics (or both) can be used to provide some degree of analgesia. Hyperalgesia has been associated with intrathecal infusion of morphine in large doses (more than 30 mg/day). This paradoxical effect is thought to be secondary to a nonopioid mechanism and can be managed by reducing the morphine dose.²² Otherwise, side effects of perispinal opioids are rare in opioid-tolerant patients. Most problems relate to managing pump refills and nursing care of catheters and catheter insertion sites, which is reflected in the significant cost of this technique.

Adding a local anesthetic (eg, bupivacaine) to morphine via the epidural route has been successful in providing good analgesia in patients whose pain was resistant to epidural morphine alone, despite high doses. In a study involving 1,205 patients, epidural morphine was used in 16 cases of unsatisfactory analgesia despite

aggressive systemic opioid therapy.²⁶ While epidural morphine was successful in 6 of 16 patients, adding small doses of bupivacaine (ie, 5 to 10 mg/hr) provided good pain relief in all 10 of the remaining patients. This study illustrates that

most patients with pain of terminal malignancies can be adequately managed without resorting to perispinal opioid therapy. Further clinical studies and trials will still be required to judge the safety, efficacy, and extended role of the perispinal route in chronic cancer and noncancer pain and, more importantly, to define in which patients this technique is best indicated.

Conclusions

For the patient with cancer pain, the oral route of opioid delivery should be the first choice (Table 3). If the oral route cannot be used because of gastrointestinal obstruction and/or severe nausea/vomiting, the rectal (or ostial route) is equivalent. Whether the oral or rectal route is used, long-acting oral preparations should be used around the clock, with "immediate" release preparation available to treat breakthrough pain. Another noninvasive alternative to the oral route is the transdermal route, which at present is available only for continuous administration of fentanyl. For treatment of breakthrough pain in a patient unable to take oral or rectal medications, a transmucosal preparation of fentanyl is now available. For those patients in whom oral, rectal, and transdermal opioids are not appropriate, subcutaneous, patient-controlled analgesia is effective and provides approximately 80% bioavailability of administered opioids. It does not require intravenous access and is relatively easy to administer. Intravenous administration of opioids is an option in those patients in whom no other route is available and who have intravenous access. The perispinal (neuraxial) route can be attempted when the oral and other parenteral routes have been unsuccessful. This route may be most successful when opioids and local anaesthetics and/or clonidine are used in combination.

Whatever route is used, administration of opioids to manage cancer pain requires knowledge of potency relative to morphine and bioavailability of the route chosen. Dose-equivalent tables are only close approximations and substantial interpatient variability is often observed. Therefore, patients should be closely followed and doses titrated to minimize side effects whenever the opioid, route, or dose is changed.

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