The Role of Opioids in Cancer Pain Management

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Abstract: Opioids remain an important cornerstone in the treatment of cancer pain. Effective analgesia is obtained in the majority of cancer pain patients with the application of fairly straightforward algorithms using opioids as the main therapy. Many rational treatment algorithms exist. In this tutorial we will describe the role of opioids in the treatment of cancer pain, including a brief overview of cancer pain syndromes, essential aspects of opioid therapy, opioid pharmacology, opioid rotation, properties of the individual opioids, and management of common side effects of opioids.

Key Words: cancer pain, opioids, opioid rotation

INTRODUCTION

Studies report that 33% of patients receiving active cancer treatment experience severe cancer-related pain. Advanced disease is associated with greater pain. Despite a recent increase in the necessity of satisfactory pain treatment practices, there is still a substantial undertreatment of cancer-related pain. Reports from outpatient settings show that 50% of patients receive inadequate treatment for pain control and approximately 30% do not receive the appropriate pharmacologic management for their pain. It has been reported that up to 25% of cancer patients in the United States die without adequate pain control. The reasons that most commonly account for the undertreatment of cancer-associated pain are often related to deficient knowledge in opioid therapy, such as overestimating the risk of addiction and of the side effects of opioids. The subjectivity associated with the pain experience is another factor that accounts for the difficulty in adequately assessing the dose of opioids necessary to control for nociception. However, this situation is probably somewhat different in comprehensive cancer centers, including MD Anderson, where the culture of increased awareness has been cultivated in the past decade. A recent informal survey of patient satisfaction in regards to the treatment of cancer-related pain demonstrated that 80% of treated patients find their pain control to be satisfactory (unpublished data).

OVERVIEW OF CANCER-RELATED PAIN

In an effort to better understand the available treatment options for pain, we will briefly discuss pain syndromes that arise as a result of cancer. Specifically, it has been estimated that two-thirds of patients with cancer have pain related to the disease itself. Another third of patients develop pain syndromes as sequelae of cancer treatment, such as chemotherapy, radiation, surgery, adjuvant, and hormonal therapy.

In most cases cancer pain stems from the tumor itself. Tumors cause pain attributed to invasion of bone, soft tissue, muscle, and nervous structures. Specifically, in some cases, rapid tumor growth or lysis can result in acute pain. A less frequent cause of cancer pain is treatment-related pain—including postchemotherapy
neuropathic pain, postsurgical pain syndromes, and postradiation pain syndromes. A thorough examination to determine the etiology of the pain will assist in successful management. The molecular basis of nociception as a result of cancer is currently being elucidated, with the long-range goal to achieve adequate relief with simpler and more focused therapeutic regimens.\(^5\)

Pain can be further classified into the broad categories of nociceptive vs. neuropathic pain. Nociceptive pain may be either somatic or visceral in origin. Some common examples of nociceptive somatic pain include bone metastasis and vertebral compression fractures. Classical nociceptive visceral pain includes pancreatic cancer pain. Neuropathic pain is seen with chemotherapy-induced painful peripheral neuropathies, postherpetic neuralgias, phantom limb pain, and others. Nociceptive syndromes are typically opioid responsive, whereas in neuropathic pain states adjuvant analgesics may be needed to obtain adequate analgesia.\(^3\)

Generally long acting opioids are used to control persistent (constant) pain and short-acting opioids intended to control breakthrough pain. According to Portenoy et al. breakthrough pain is defined as a “transitory exacerbation of pain that occurs on a background of otherwise stable persistent pain.”\(^6\) Breakthrough pain may be caused by somatic, visceral, or neuropathic nociceptive input and is most often in the same area as the constant pain. The episodes are severe and paroxysmal and may last from a few minutes to a few hours. Breakthrough pain may be movement-related (incident pain), or occur without provocation (spontaneous pain), or occur toward the end of a dosing interval (end-of-dose failure).

**BASIC PRINCIPLES OF OPIOID THERAPY**

Opioids remain the cornerstone of pharmacotherapy for cancer treatment. In the last decade, an increase in the number of opioid agents and formulations available for the treatment of chronic pain have provided physicians with a greater range of pharmacologic analgesic options.\(^7\) The three-step analgesic ladder developed by the World Health Organization (WHO, 1986) under the leadership of Dr. Kathy Foley is the first widely accepted model in the treatment of cancer pain\(^8\) (Figure 1). The WHO guidelines, and some follow-up guidelines including the National Cancer Care Network (NCCN)\(^9\) provide a fairly simple algorithm for the treatment of cancer pain based on patients’ self-report of symptom severity.

Non-opioid agents, such as, nonsteroidal anti-inflammatories (NSAIDS) or acetaminophen are recommended for the treatment of mild pain (first step of the ladder). For neuropathic pain syndromes, adjuvant medications, which include anticonvulsant and antidepressant medications, are often recommended. However, when these treatments fail to provide adequate relief, a *weak opioid*, such as codeine, hydrocodone, tramadol, and propoxyphene is used. This group of opioids is used in the management of mild to moderate pain (second step of the WHO analgesic ladder). The third step of the analgesic ladder (moderate to severe pain) includes *strong opioids*, such as morphine, hydromorphone, oxycodone, and fentanyl.

In subsequent years, the WHO guidelines have been expanded in an effort to achieve optimum treatment regimens. Specifically, the WHO analgesic ladder recommends the oral route as the most preferable route of opioid administration. Analgesics should be given “by the clock,” meaning at fixed-time intervals. This allows for the subsequent dose to be given before the effect of the previous one has fully worn off, so that pain relief is provided continuously. Opioid therapy should be individualized, as there is interindividual variability in opioid metabolism, and pain intensity and tolerance, and thus, response to opioid treatment.\(^10\) Application of WHO guidelines has been shown to provide adequate
pain relief in up to 90%\textsuperscript{11} of patients depending on the definitions of “adequate.” Many feel that the WHO ladder was needed politically to allow adoption of opioids into many traditionally opioid-phobic countries worldwide. In practice, most practitioners agree that cancer patients need not progress through all the stages of WHO ladder, with strong opioids initiated sooner in the course of treatment.\textsuperscript{12}

Another recent approach in the use of guidelines includes the concept of using a numerical pain scale (0 to 10) to help quantify the patient’s pain and guide treatment with the appropriate analgesic regimen. We have incorporated this idea into our own MD Anderson cancer pain treatment guidelines (Figure 2). The use of a numerical pain rating may help in trending the patient's response to therapy. Several points should be made about these numbers: first, one of the concerns about recommending treatment based on the scale is that it appears to emphasize the number, and the clinician should be wary of viewing them as prescriptive or bypassing a comprehensive assessment. However, this numerical rating scale is very helpful for patients in describing their pain levels, especially in cases where language, age, or other communication barriers may exist.

Currently a wide variety of opioids are used in medical practice. Clinical pharmacology categorizes opioids into controlled release (CR) (MS Contin\textsuperscript{®}, Avinza\textsuperscript{®}, Kadian\textsuperscript{®}, Oxycontin\textsuperscript{®}, Duragesic\textsuperscript{®}, etc.) and immediate release (IR) (MSIR, Oxycodone, Hydromorphone, Actiq\textsuperscript{®}). CR opioids provide sustained opioid plasma levels of medication over a period of 8 to 24 hours, depending on their formulation. The properties of individual CR opioids will be reviewed later in this tutorial.

Patients with cancer pain who have failed to respond to mild opioids or who have a significant disease burden should be started on potent IR opioids, administered around the clock with extra doses if needed.\textsuperscript{4} Although around-the-clock dosing is preferable, as-needed dosing alone should be considered in relatively opioid-naïve patients, patients with rapidly changing pain, or patients with intermittent pain.\textsuperscript{13} For patients with severe pain, rapid titration with i.v. opioids in the form of an i.v. Patient controlled analgesia (PCA) might be necessary to achieve a desirable level of pain control. Oral transmucosal fentanyl is another option for these patients.\textsuperscript{14} When the desired level of comfort is achieved, adequate analgesia can be maintained by using long-acting opioid for baseline pain, and short-acting opioid for breakthrough pain.

**OPIOID RECEPTORS**

In vivo, opioids produce their effect by binding to opioid receptors. At the molecular level the opioid receptors are 7 transmembrane spanning, G protein linked complexes, which inhibit target cell activity. Endogenous and exogenous opioid agonists act in the central nervous system (CNS) by binding to \(\mu\) (mu), \(\kappa\) (kappa), and \(\delta\) (delta) receptors.\textsuperscript{15} Opioid receptors are distributed throughout the brain, spinal cord, and the gut. The localization of opioid receptors in the brain was not known until 1973, when group of researchers demonstrated their existence in several species, including man by the use of a radioligand binding assay.\textsuperscript{16}

The analgesic effect is mediated through a complex interaction of \(\mu\), \(\delta\), and \(\kappa\) receptors, which can be antagonized by nalaxone. Opioid-induced analgesia is the result of ligand-receptor CNS activity at the spinal and supraspinal level.\textsuperscript{17} General analgesia is induced by the \(\mu\) receptors, which beyond their analgesic effect also mediate urinary retention, euphoria, constipation, miosis, temperature increase, and physical dependence. The \(\mu\) receptor has two isoforms: the \(\mu_1\) receptor, the affinity of which is the same for all opioids, while \(\mu_2\) has greater selectivity for morphine. Endogenously the \(\mu\) receptors bind to naturally occurring ligands, endorphins. Kappa receptors, which endogenously bind to dynorphins, are responsible for spinal analgesia and sedation. The delta receptors, the natural ligand of which is leu-enkephaline, is thought to be responsible for the modulation of \(\mu_1\) receptor activity, such as physical dependence.\textsuperscript{18}

**OPIOID ROTATION AND EQUIANALGESIC RATIOS**

Patients who experience poor analgesia or significant side effects may benefit from a change in their opioids, called “opioid rotation.” This approach is based on the observation that interindividual response varies remarkably from opioid to opioid and that switching to another opioid may lead to a better opioid responsiveness with fewer side effects.\textsuperscript{19} Opioid rotation involves discontinuation of the previously used opioid and initiation of the new one at the equianalgesic dose. Opioid rotation can be accomplished in a variety of ways. Different strategies have been described in the literature. In our institution the pharmacologic evaluation begins with the calculation of the morphine equivalent daily dose (MEDD) by conversion of all the opioids taken into the oral morphine equivalent dose expressed in milligrams.\textsuperscript{20} Equianalgesic ratios provided in the Table 1 are used to calculate MEDD. If a patient is
Cancer Pain

Components of Comprehensive Pain Assessment:
1. Evaluation of pain. Determine level using 0–10 intensity scale, location, onset, duration, frequency, quality (somatic, visceral, neuropathic), history, etiology, associated symptoms, what modifies the pain, side effects associated with treatment of pain, and response to other pain medications.
   - No pain (0) Mild (1–3) Moderate (4–6) or Severe (7–10)
2. Evaluation of past medical history (oncologic or other significant medical illnesses) to include medication history.

Nonsteroidal anti-inflammatory drugs (including Cox-2 agents) and acetaminophen
- If ineffective: opioids (hydrocodone or scheduled or as needed)

Oral opioids:
- Morphine, 10 mg orally, every 4 hours as needed or scheduled
- Oxycodone, 5 mg orally, every 4 hours as needed or scheduled
- Adjuvants: Nonsteroidal anti-inflammatory drugs, antidepressants, antiepileptics, etc.

Overall reassessment in 24 to 48 hours

Reassess frequently based on clinical situation

Overall reassessment at each subsequent visit or interaction

Managing pain related to oncologic emergencies, if any

Reevaluate opioid titration
Reevaluate pain diagnosis
Consider consults from specialty services***

All patients receiving opioids should begin:
- Bowel regimen (such as oral Senna, 1 tablet twice daily)
- Antiemetics as needed (such as metoclopramide, 10 mg, 30 minutes before meals and bedtime)
- Constitutional symptoms as needed (such as metoprolamide 10 mg, 30 minutes before meals and bedtime)
- Educational activities regarding pain management
- Psychosocial support as needed

Consider conversion to a sustained-release agent with rescue medications
Continue adequants or add them as needed
Reassess and modify side effects of pain treatment
Provide psychosocial support
Provide educational activities
Reassess pain every week until comfortable, then every visit

Guidelines Change Over Time - For Updates Refer to www.mdanderson.org

*Pain related to an oncologic emergency requires assessment and treatment (e.g., surgery, steroids, radiotherapy, antibiotics) along with an emergent consultation. Oncologic emergencies include:
- Bowel obstruction/perforation
- Fracture or impending fracture of weight-bearing bone
- Brain metastasis
- Leptomeningeal metastasis
- Epidural metastasis/spinal cord compression
- Pain related to infection

**Some patients with chronic pain syndromes will report high pain scores on an ongoing basis. Generally, this situation is not a crisis.

***Consult the Postoperative Pain Service, Cancer Pain Section, Department of Symptom Control and Palliative Care, or other specialties as needed (e.g., Radiotherapy).

Figure 2. MD Anderson cancer pain algorithm.
receiving opioids in the i.v. form 1 mg (i.v.) to 2.5 mg (p.o.) ratio should be factored in.

Following calculations of the MEDD a resulting dose of the new opioid is then reduced by 30% to account for incomplete cross-tolerance and interindividual variability in potency of individual opioids.\(^{21}\) Deciding the rationale for dividing the calculated dose into sustained-release and immediate-release tablets is largely an empiric choice. A reasonable size of rescue dose can range from 5% to 15% of the total daily dose.\(^{19}\)

**OPIOIDS FOR MILD TO MODERATE PAIN**

**Tramadol**

Tramadol is a synthetic opioid analgesic that is a racemic mixture of two isomers with weak affinity for \(\mu\) receptor. Tramadol is also a norepinephrine and selective serotonin reuptake inhibitor and has the advantage of additional nonopioid central effects.\(^{4}\) The affinity of tramadol for the \(\mu\) (\(\mu\)) receptor is approximately 6000 times weaker than that of morphine and 10 times weaker than codeine. Tramadol is metabolized by cytochrome P450 (CYP) 2D6 with resultant O-desmethyl metabolite having approximately 200-fold higher activity for opioid receptors than the parent compound.\(^{22}\) Tramadol (Ultram) is available as 50 mg IR tablets. Oral tramadol (200 to 400 mg/day) is considered effective and safe in treatment of cancer pain.\(^{23}\) The equianalgesic ratio of Ultram to morphine is approximately 5:1. Similarly to other opioids used for treatment of mild to moderate pain, tramadol is also available in combination with acetaminophen (Ultracet) (tramadol 37.5 mg/acetaminophen 325 mg). The addition of acetaminophen to tramadol provides synergistic analgesia. Ultracet has not been studied extensively in cancer patients.

**Codeine**

Codeine is an opium alkaloid that is available as single agent or in combination with other analgesics. Codeine is metabolized to active drug by P450 (CYP) 2D6.\(^{24}\) The analgesic effect of codeine is largely attributed to the production of its active metabolite morphine. Codeine’s potency is 1/10 of morphine. Poor metabolizers, patients with low or undetectable CYP2D, derive no analgesic effect from codeine. Codeine is effective in treatment of mild to moderate cancer pain but has no role in treatment of severe pain.\(^{25}\)

**Hydrocodone**

Hydrocodone is the hydrogenated ketone derivative of codeine. Hydrocodone is typically available only as a combination product with acetaminophen or aspirin, thus limiting its usefulness in treatment of cancer pain. Hydrocodone is metabolized by CYP2D6 to an active metabolite hydromorphone, which has strong \(\mu\) receptor activity and may mediate hydrocodone’s pharmacologic effect.\(^{26}\) Although traditionally thought of as a week opioid with equianalgesic ratio to morphine of 1:0.15 hydrocodone might be significantly more potent. Some practitioners feel that a ratio of 1:0.5 is more accurate. Combinations of hydrocodone and acetaminophen are available in a variety of strengths: Vicodin 7.5/500, Vicodin (5/500), Vicodin ES (7.5/750), Vicodin HP (10/660), Norco (5/325, 7.5/325, 10/325). In patients with preexisting liver disease Vicoprophen (7.5 hydrocodone/200 mg ibuprophen) may be useful as a short-acting opioid.

**OPIOIDS FOR MODERATE TO SEVERE PAIN**

**Morphine**

Morphine is considered to be a prototype opioid agent. The WHO expert committee considers morphine a major pain-relieving compound and advocates for its wide global availability for treatment of cancer-related pain.\(^{8}\) The liver is the principal site of morphine metabolism. Morphine undergoes a significant first-pass metabolism resulting in the production of three metabolites: normorphine, morphine-3-glucuronide (M3G), and morphine-6-glucuronide (M6G). The UDP-glucuronosyl-

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**Table 1. Conversion Table for Opioids**

<table>
<thead>
<tr>
<th>Opioid</th>
<th>From Parenteral Opioid to Parenteral Morphine</th>
<th>From Same Parenteral Opioid to Oral Opioid</th>
<th>From Oral Opioid to Oral Morphine</th>
<th>From Oral Morphine to Oral Opioid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>1</td>
<td>2.5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>5</td>
<td>2</td>
<td>5</td>
<td>0.2</td>
</tr>
<tr>
<td>Meperidine (rarely used)</td>
<td>0.13</td>
<td>4</td>
<td>0.1</td>
<td>10</td>
</tr>
<tr>
<td>Codeine (rarely used)</td>
<td>N/A</td>
<td>N/A</td>
<td>0.15</td>
<td>7</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>N/A</td>
<td>N/A</td>
<td>1.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>N/A</td>
<td>N/A</td>
<td>0.15–0.5</td>
<td>7</td>
</tr>
</tbody>
</table>
transferase (UGT) is a major metabolizing enzyme.\textsuperscript{28} M3G is a main product of metabolism; it is devoid of analgesic activity. Recent research has demonstrated that M3G may be responsible for some of the morphine-associated neurotoxicity (see below). M6G is a hydrophilic metabolite with poor CNS penetration that is significantly more potent then morphine. If administered intrathecally it has 90- to 650-fold analgesic potency of morphine.\textsuperscript{29} The products of morphine metabolism are eliminated by kidney, thus compromised renal status may lead to accumulation of metabolites resulting in neurotoxicity. Morphine should be used cautiously in patients with renal impairment.\textsuperscript{29} The elimination half-life of morphine is approximately 2 hours.

Morphine can be administered via oral, rectal, sublingual, i.v., subcutaneous, topical, epidural, and intrathecal routes. Oral is the preferred route. Intrathecal and epidural morphine are approximately 100 and 10 times, respectively, more potent than oral. Epidural and intrathecal routes allow to bypass first-pass metabolism, and very little of morphine metabolites are found in CSF.

Morphine metabolism can be induced or inhibited by a variety of medications. Carbamazepine, phenobarbital, phenytoin, and rifampin induce UGT enzyme and accelerate clearance of morphine. Phenothiazines, tricyclic antidepressants, and cimetidine interfere with morphine metabolism and increase the effect of morphine. Lorazepam and other benzodiazepines that undergo glucuronidation competitively inhibit morphine metabolism. Coadministration of morphine and benzodiazepines may produce synergistic action resulting in sedation, hypotension, and sometimes delirium.\textsuperscript{29}

Optimal management of pain via an oral route requires coadministration of long (CR) and short (IR) acting morphine.\textsuperscript{30} IR formulations are used for initial dose titration and treatment of breakthrough pain. They can be administered on as needed basis or around the clock. The doses then can be adjusted based on the amount of the breakthrough medication. An increase in dose is generally well tolerated, as morphine does not have a ceiling effect. Once the optimal dose is determined, a CR may be started for maintenance treatment to be administered at intervals of 8 to 12 hours. IR continues to be used to control breakthrough pain.

IR morphine is available as 15 and 30 mg tablets and as a solution of different strength. CR morphine is available as a generic or brand names (MS Contin®, Kadian®, Oramorph SR®, and Avinza®). MS Contin® was introduced in the U.K. in 1981 as the first CR opioid. This formulation is based on a dual-control matrix (Contin) that uses two different types of retarding polymers, which provide slow release matrix. MS Contin® is available in 15, 30, 60, 100, and 200 mg tablets. Kadian® is a morphine sulfate preparation that is contained in a closed hard gelatin capsule with a polymer-coated shell. The capsule consists of three primary layers. The inner layer is composed of a sugar core. A second layer that is a morphine sulfate binding layer surrounds the inner layer. The outer layer consists of a sustained-release pH-dependent polymer-coated shell. The sustained-release properties are derived from the polymer coating that is pH-activated and its degradation allows the formation of pores that release the morphine sulfate. The rate of morphine sulfate release is based on the interaction of polymer-coated shell and the digestive juices. Kadian is available as 20, 30, 50, 60, and 100 mg tablets. Avinza®, a once-a-day morphine, is a novel type of medication based on SODAS™ technology. Avinza® is composed of 2 types of beads within a hard gelatin capsule shell. IR beads (10%) provide a quick release of morphine to rapidly achieve target plasma morphine concentrations within 30 minutes. Sustained-release beads (90%) slowly release morphine to maintain target plasma morphine concentrations during a 24-hour dosing interval. Avinza® is available as 30, 60, 90, and 120 mg tablets.

**Hydromorphone (Dilaudid)**

Hydromorphone is a semisynthetic opioid that has been available for clinical use since 1926. Similarly to morphine, when administered by oral route it undergoes an extensive first-pass metabolism, resulting in production of 3 major metabolites: hydromorphone-3-glucuronide (H-3-G), dihydromorphine, and dihydroisomorphine. H3G is an inactive metabolite; the other two may have greater analgesic activity than the parent compound.\textsuperscript{31} Hydromorphone’s bioavailability is less than morphine, but hydromorphone is more soluble than morphine.

In the United States, hydromorphone is available as IR tablet (1 mg, 2 mg, 3 mg, 4 mg, and 8 mg), liquid (5 mg/5 mL), and suppositories. Sustained-release tablets are not available in U.S.A., but available elsewhere. Hydromorphone acts on \(\mu\) (\(\mu\)) and delta receptors, it has no effect on kappa. Hydromorphone and its metabolites are eliminated by kidney. In the setting of renal failure hydromorphone and its byproducts will accumulate, resulting in opioid toxicity. There is no clear consensus whether hydromorphone is preferred to
morphine in renal impairment. A recent retrospective study demonstrated that hydromorphone is safe and effective in patients with renal impairment (including those with end-stage disease). Hydromorphone interacts with other medications, which can potentiate or reduce its effect. Hydromorphone relieves continuous dull pain more effectively than sharp intermittent pain. However, when taken at higher doses, it can be effective for treatment of even severe pain associated with renal and biliary colic. Hydromorphone can be administered via epidural and intrathecal routes. When mixed with epinephrine it provides superior pain relief.

The initial recommend dose of hydromorphone in the opioid-naive cancer patient is 1 to 3 mg p.o. every 3 to 4 hours, with subsequent cancer dose titration as clinically indicated. For opioid rotation 5:1 (morphine:hydromorphone) ratio is generally used, although a ratio of 7.5:1 has been also reported in the literature. Hydromorphone and morphine have similar side effect profiles, however, pruritis, sedation, nausea, and vomiting are less common with hydromorphone.

Oxycodone

Oxycodone, a derivative of thebaine, has been in clinical use for over then 80 years. It differs from morphine in its pharmacokinetic and pharmacodynamic properties. Oxycodone is subject to the first-pass effect. It is metabolized by cytochrome P450 enzyme CYP2D6 to oxymorphone and the dominant nonactive metabolite noroxycodone. Oxymorphone is a potent analgesic, however, it accounts only for 10% of oxycodone metabolism. Unlike morphine, oxycodone’s anticoceptive activity is partly mediated by the κ (kappa) receptor. The effect of κ receptor might explain the observation that coadministration of sub-antinociceptive doses of oxycodone and morphine in experimental animals results in greater synergistic effect. Intraspinal oxycodone, however, has a different effect; it appears to antagonize morphine and reduce its analgesic effect.

Oxycodone can be administered via oral, rectal, intramuscular, intravenous, intranasal, sublingual, and intraspinal routes. Oral oxycodone is available in IR and CR formulations. CR oxycodone (Oxycontin®) is absorbed in bi-exponential fashion: a rapid phase during which approximately 40% of drug is absorbed and a slow phase with a half-life of 6.2 h. Oxycontin® is based on an AcroContin drug delivery system. The AcroContin system uses a dual-control matrix with two hydrophobic polymers, which are not influenced by pH. Thus, dissolution profile of Oxycontin® is independent of acidity. Oral bioavailability is similar for IR and CR formulations. Oxycodone is renally eliminated, and in renal failure its clearance is diminished. In cirrhosis and end-stage liver disease, oxycodone metabolism is significantly slowed, thus care must be exercised in this patient population.

Equianalgesic ratio between oxycodone and morphine is 1:1.5. There is an incomplete cross-tolerance between oxycodone and other opioids: appropriate reductions should be made when rotating opioids. CR oxycodone is effective in moderate to severe cancer pain and allows for convenience of every 12 hours administration. If end of dose failure occurs CR oxycodone can be administered every 8 hours.

Use of Oxycontin® has been somewhat hampered by recent negative publicity. A 5.2 billion dollar class-action lawsuit has been brought against makers of the Oxycontin®. The lawsuit alleges that the company failed to inform consumers about “unique” addiction potential of the drug. Multiple studies demonstrated that the addiction potential of Oxycontin® is similar to other opioids. In fact, drug abusers destroy the delivery system of Oxycontin® by crushing it and then inhaling or injecting extracted oxycodone. There is conclusive evidence that oxycodone’s kappa receptor activity does not contribute to increased addiction risks.

Oxycodone interacts with several medications, including selective serotonin uptake inhibitors (SSRIs), cyclosporine, and rifampin. SSRIs inhibit oxycodone metabolism by cytochrome P450, which leads to higher concentration and increased toxicity. Visual hallucinations and tremors have been reported with oxycodone dose titration on stable doses of sertraline.

The side effect profile of oxycodone is similar to other opioids. There are fewer hallucinations associated with oxycodone than with other opioids.

Fentanyl

Fentanyl is a semisynthetic opioid with high degree of lipid solubility. Fentanyl has an established role as I.V. anesthetic and analgesic drug. Fentanyl is 75 to 100 times as potent as morphine. Fentanyl is metabolized by the liver to phenylacetic acid, norfentanyl and small amount of pharmacologically active hydroxyl fentanyl. In treatment of cancer-related pain, transdermal and transmucosal routes are most commonly used.

Fentanyl’s low molecular weight and high lipophilicility make it a good candidate for transdermal administration. DURAGESIC® is a rectangular transparent unit comprising of a protective liner and 4 functional
layers. DURAGESIC® (fentanyl transdermal system) releases fentanyl from the reservoir at a nearly constant amount per unit time. The concentration gradient existing between the saturated solution of drug in the reservoir and the lower concentration in the skin drives drug release. Fentanyl moves in the direction of the lower concentration at a rate determined by the copolymer release membrane and the diffusion of fentanyl through the skin layers. While the actual rate of fentanyl delivery to the skin varies over the 72-hour application period, each system is labeled with a nominal flux that represents the average amount of drug delivered to the systemic circulation per hour across average skin. If the DURAGESIC® system is cut or damaged, controlled drug delivery will not be possible. An equivalency ratio of 100:1 (oral morphine in milligrams per 24 hours:fentanyl transdermal patch in milligrams per 24 hours) is suggested by several authors. For convenience purposes a conversion table can be used (Table 2).

Oral transmucosal fentanyl citrate OTFC (Actiq®) is a potent formulation of fentanyl manufactured in a matrix of sucrose and liquid glucose base and fitted onto radioopaque plastic handle and absorbed via oral mucosa. In U.S.A. Actiq® is approved by Food and Drug Administration (FDA) for treatment of breakthrough pain in opioid-tolerant patients with cancer. It is available in 6 different strength: 200 μg, 400 μg, 600 μg, 800 μg, 1200 μg, and 1600 μg. Although there is some off label use of Actiq®, it is not recommended for treatment of acute and postoperative pain. At this point there is not enough data to determine a relationship between the total daily dose of the fixed schedule opioid regimen and the dose of Actiq® required to manage breakthrough pain. OTFC 200 μg approximately equals 2 mg i.v. morphine; OTFC 800 μg approximately equals 10 mg of i.v. morphine. Recent retrospective case series demonstrated that OTFC might be an effective alternative over intravenous opioids to rapidly titrate analgesia in selected opioid-tolerant cancer patients experiencing pain crisis.14

<table>
<thead>
<tr>
<th>Table 2. Transdermal Fentanyl Dosing Guidelines</th>
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<tbody>
<tr>
<td>i.v./s.c. Morphine</td>
</tr>
<tr>
<td>--------------------</td>
</tr>
<tr>
<td>20 mg</td>
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<tr>
<td>40 mg</td>
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<tr>
<td>60 mg</td>
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<td>80 mg</td>
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</table>

Methadone

Methadone is a synthetic opioid with a unique set of properties distinguishing it from other opioids. Although it has been used mostly as maintenance drug for addicts, in the last 10 to 15 years its use as an analgesic agent has dramatically increased. Methadone acts on μ, δ receptors, and NMDA receptors. Excitatory amino acids such as NMDA have been implicated in the development of opioid resistance of neuropathic pain. Because of its NMDA receptor activity, methadone might have a special role in treatment of neuropathic pain.40

In most countries, including the U.S.A., methadone is available in racemic form. 1-methadone is twice as potent as the racemic form. Methadone is mainly administered via oral, rectal, and parenteral routes. Subcutaneous route is associated with local reactions. Individual practitioners also use it intrathecally, but the safety of this route is not well established. Oral methadone is supplied as 5 and 10 mg tablets, 40 mg tab liquid form (10 mg/mL), and powder form, which can be used for the preparations of oral and rectal solutions.

Methadone is extensively metabolized in the liver by cytochrome P450 CYP 3A3/4 isoenzyme to inactive metabolites. Including its activity at NMDA receptor methadone has a number of advantages over other opioids. Methadone has a very good bioavailability via all routes of administration. It has no known metabolites and excreted mainly by fecal route, hence does not accumulate in renal failure. Among the disadvantages of methadone is its long and unpredictable elimination half-life, which may lead to significant side effects, especially respiratory depression.41

Equianalgesic ratios between morphine (and other opioids) to methadone are dose-dependent. These ratios may vary from 1:1 at low doses of oral opioid to as high as 20:1 for patients receiving oral morphine in excess of 300 mg per day. Because of the wide variability of equianalgesic ratios opioid rotation to methadone is difficult. Toxicity of methadone tends to occur more frequently in patients previously exposed to high doses of opioids than in patients receiving low dose. Several rotation strategies have been proposed in the literature.42 Some practitioners advocate a method of immediate discontinuation of morphine and rotation to methadone administered every 8 hours with following equianalgesic ratios: morphine <90 mg/day (4:1), morphine 90 to 300 mg/day (8:1), and morphine >300 mg/
day (12:1). Nauk et al. suggested a different method. He also proposes an immediate discontinuation of morphine, but methadone is administered every 4 hours. On the first day of rotation morphine will be stopped and methadone initiated at 5 to 10 mg every 4 hours and every hour as needed. On days 2 and 3 the dose of methadone will be increased by up to 30% every 4 hours and every hour as needed until pain relief is obtained and no side effects occur. On the day 4 the dosing interval should be increased to every 8 hours and every 3 hours as needed at the same total daily dose used on day 3. If necessary the dose should be increased by 30% until pain relief is obtained and no side effects occur. Another method proposed by Bruera advocates for gradual decrease of morphine (MEDD >100 mg) in course of 3 days.41 On the first day the dose of the opioid is reduced by 30% to 50% and methadone is initiated at 10:1 ratio. On the second day the dose of the initial opioid should be reduced by another 30% to 50%, and the dose of methadone is titrated to the symptom. On the day 3 initial opioid is discontinued and methadone dose is maintained every 8 hours with the use of rescue medication for breakthrough pain. In patients with MEDD less than 100 mg immediate switch to methadone 5 mg every 8 hours and every 2 hours for breakthrough pain. The relatively long half-life of methadone allows every 8 hours administration for adequate pain control. There is also emerging evidence that every 12 hours schedule is appropriate for adequate pain control.

COMMON SIDE EFFECTS OF OPIOIDS AND TREATMENT

Dry mouth (xerostomia), is common, with overall prevalence of 77% of patients taking morphine. It might be exacerbated by coadministration of antidepressant or anticholinergic drugs. Mouth care with sodium bicarbonate is recommended. Pilocarpine 2% eye drops by mouth or 5 mg by mouth 3 times daily may reduce opioid-induced xerostomia.29

Opioids can cause nausea and vomiting, especially after initiation or increase in dose. This usually responds well to antiemetics and disappears after 3 to 4 days.44 Many cancer patients have underlying nausea prior to opioid administration. Pain itself can cause nausea and vomiting. A variety of antiemetics are available. In our practice we frequently use metoclopramide (Reglan) 10 mg p.o. qid 30 minutes before meals and qhs. The etiology of nausea is frequently multifactorial including metabolic abnormalities, chemotherapy/ radiotherapy, bowel obstruction, peptic ulcer disease, and so forth.

Constipation should be anticipated and treated proactively at the beginning of opioid therapy. Opioid-induced constipation can be treated by stool softener (docusate sodium 100 mg tid) and/or colonic stimulant (senna 1 tabs p.o. daily). In our practice Senekot-S, a combination product of stimulant and stool softener is frequently used. SENOKOT-S tablets are designed to relieve both aspects of functional constipation—bowel inertia and hard, dry stools. They provide a natural neuroperistaltic stimulant combined with a classic stool softener, standardized senna concentrate, which gently stimulates the colon while docusate sodium softens the stool for smoother and easier evacuation. This coordinated dual action of the two ingredients results in colonspecific, predictable laxative effect, generally producing bowel movement in 6 to 12 hours. Flexibility of dosage permits adjustment to individual requirements (PDR). Initial dose is 1 tab bid. If constipation persists Lactulose can be initiated. KRISTALOSE™ (Lactulose) is a synthetic disaccharide in the form of crystals for reconstitution prior to use for oral administration. Each 10 g of lactulose contains less than 0.3 g galactose and lactose as a total sum. The pH range is 3.0 to 7.0. Lactulose is a colonic acidifier, which promotes laxation (PDR). An amount of 15 to 30 cc is administered p.o. every 4 hour until bowel movement, with subsequent dosing once a day.

Sedation is a common symptom in opioid-naive patients after initiation of treatment. However, this rarely lasts beyond 48 to 72 hours after analgesia is achieved. In some patients with severe pain somnolence during the first days of treatment or after increase in dose may simply reflect increased comfort after days of insomnia precipitated by pain. Sedation can be treated with adjuvant medications. Methylphenidate (Ritalin) 5 mg in AM and 5 mg at noon can be used. Alternatively sedation can be treated with modafinil (Provigil) starting 100 mg in AM and titrating 100 mg BID or 200 q AM.

Opioid-induced neurotoxicity (OIN) is a syndrome that has been recently described by Bruera et al.4 Its features include cognitive impairment, severe sedation, hallucinations, delirium, myoclonus, seizure, hyperalgesia, and allodynia. The symptoms of OIN are mainly seen in patients on chronic high-doses opioids, or in a setting of fluid depletion and renal failure. Opioid rotation, adequate hydration, and dose reduction is recommended for treatment.
CONCLUSION

Opioids are the main pharmacologic therapy for cancer-related pain syndromes. A number of algorithms exist to guide the use of long- and short-acting opioids for optimal effect. In some patients, opioid doses are limited by intolerable side effects including sedation, confusion, constipation, nausea, and pruritis. These side effects are best managed by changing opioids, adding agents to treat the side effect, or using neuraxial analgesia or neural blockade to lower systemic opioids doses.45–48

Some basic tenets of cancer pain management include the use of:

- Oral opioids (or transdermal) whenever possible;
- Combinations of long-acting opioids for constant pain with short-acting opioids for "breakthrough" pain;
- Adjuvant coanalgesics including NSAIDs, anticonvulsants, antidepressants, and topicals to minimize opioid doses and concomitant opioid-related side effects;
- Prophylactic treatment of constipation and nausea; and
- Blocks, parenteral infusions, neuraxial infusions, palliative radiotherapy, palliative chemotherapy, and surgery in combination for optimal patient quality of life (the "art" of oncology).

In most cases, adequate pain and symptom control can be obtained through regular assessment and application of the relatively straightforward principles outlined above.

REFERENCES

34. Paul D, Standifer KM, Inturrisi CE, Pasternak GW. Pharmacological characterization of morphine 6-beta-


**QUESTIONS**

1. A patient has been taking long acting and immediate release morphine for cancer related pain. Her total morphine daily dose is 300 mg per day. The patient’s pain is under good control, but she complains of somnolence. Acceptable maneuvers include:

   A. Starting methylphenidate
   B. Starting modafinil
   C. Changing opioids (opioid rotation)
   D. All of the above

2. Which of the following is least safe to use in a patient with renal failure:

   A. Transdermal fentanyl
   B. Actiq (oral transmucosal fentanyl)
   C. Morphine
   D. Methadone

3. A patient is using a 100 mcg per hour Duragesic patch with a few hydrocodone for “breakthrough” pain, but due to pruritus, wishes to change opioids. Morphine worked well in the past. An acceptable regimen of morphine would be:

   A. MS immediate release 10 mg tabs, 1 PO tid
   B. MS extended release 200 mg PO q 6 hours scheduled plus MS immediate release 30 mg 1–2 tabs q 3 hours PRN
   C. MS extended release 200 mg, 2 tablets PO q 12 hours with no breakthrough dosing
   D. MS extended release 100 mg PO q 12 hours, plus MS immediate release 15 mg, 1–2 PO q 3 hours

4. A patient is using hydrocodone 5 mg, 1–2 PO q 6 hours for pain, total of 8 tablets per day. This equals 40 mg of hydrocodone and approxi-
mately oral morphine equivalent doses of 20 mg per day. The patient complains of inadequate analgesia, and appropriate “step-up” regimen would be:

A. Oxycodone—CR 10 mg PO q 12 hours scheduled, plus oxycodone 5 mg 1 to 2 PO q 4 hours PRN breakthrough pain
B. Duragesic 100 mcg/hour + hydromorphone 4 to 8 mg PO q3 hours PRN pain
C. Oxycodone—CR 80 mg PO q 6 hours scheduled
D. Methadone 40 mg PO q 6 hours scheduled

5. A unique property of oxycodone is that:
   A. it does NOT bind to mu receptor
   B. it binds only to epsilon receptor
   C. it is not metabolized by CYT P450
   D. it is not subject to the first-pass metabolism
   E. its antinociceptive activity is partially mediated by the kappa receptor

6. Which of the following opioids does NOT have a CR (controlled-release) formulation available in the USA?
   A. Morphine
   B. Hydromorphone
   C. Fentanyl
   D. Oxycodone

7. A patient has been taking Oxycontin 40 mg PO BID, and hydromorphone 4 mg 1–2 tablets q 4 h PRN (8 tablets per day). The patients oral morphine daily dose (MEDD) is:
   A. 100
   B. 120
   C. 200
   D. 280
   E. 500

8. A patient with advance breast cancer is experiencing increased pain, nausea, vomiting, fatigue and myoclonus. Until recently the patient’s pain was well controlled with MS Contin 100 mg BID and MSIR 15 mg PO q 3 hours PRN. The next logical step is:
   A. D/C opioids and start WHO analgesic ladder from step 1
   B. Immediate hospitalization and treatment with adjuvants
   C. Tell patient that symptoms she experiences are normal and no further treatment is necessary
   D. Opioid rotation

9. Which opioids may be used as breakthrough agents?
   A. morphine
   B. oxycodone
   C. methadone
   D. All of the above

10. A patient has been taking MS Contin 30 mg BID and hydrocodone 7.5 mg (2 tabs every 4 hours) and continues to have pain. An appropriate next step would be:
    A. Increase MS Contin to 30 mg TID
    B. Increase MS Contin to 45 mg BID
    C. Discontinue hydrocodone and add a stronger short acting opioid
    D. All of the above

11. In the USA, OTFC is approved by FDA for:
    A. Postoperative pain
    B. Non malignant pain crisis
    C. Breakthrough pain in opioid tolerant patients with non malignant pain
    D. Breakthrough pain in opioid tolerant patients with malignant pain

12. A patient with prostate cancer with spinal metastases has pain despite using Duragesic 300 mcg/hour patches and OTFC 600 mcg (6 per day) for breakthrough pain. Reasonable options to optimize pain management may be:
    A. Increase the dose of Duragesic and/or OTFC
    B. Add another breakthrough pain medication
    C. Opioid rotation to a different long acting opioid
    D. All of the above

Correct answers: