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Opioids for cancer pain: the challenge of optimizing treatment

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Abstract

During 2007, 11.7 million US men and women of all ages suffered from some form of invasive cancer. During their illness, at least 70% (8.2 million) will experience pain sufficiently severe to require chronic opioid treatment. Cancer-induced pain is usually described under 3 headings: acute pain, chronic pain, and breakthrough pain. Among patients with chronic, persistent cancer pain controlled by around-the-clock analgesics, there is a high prevalence of breakthrough pain—often precipitated by some form of physical activity. Breakthrough pain seems best treated by a powerful, fast-acting opioid such as intravenous morphine or transmucosal fentanyl. At present, opioids are virtually the only analgesics capable of controlling moderate and severe cancer pain. In recent years, a veritable arsenal of opioids with a wide range of pharmacologic properties has become available for use in different pain situations. The World Health Organization has developed a 3-step "analgesic ladder" to guide management of cancer pain, based on the pain's severity, estimated by means of a 1 to 10 numeric rating scale. As the severity of the pain escalates, more potent (World Health Organization Step III) opioids are used. When faced with a difficult case of cancer pain, the physician must choose—from an array of options—the safest and most effective opioid analgesic and the most appropriate delivery system. Such decisions require an adequate understanding of the available opioids and experience with their use. The pharmacodynamic response to a given opioid depends on the nature of the receptor to which the opioid binds and its affinity for the receptor. Morphine activates the μ-opioid receptors, resulting in not only analgesia and sedation, but also euphoria, respiratory depression, constipation, and pruritus. The existence of a number of opioid receptor subtypes, each with its own repertoire of responses, has given rise to the hope (as yet unrealized) that an opioid can be found (or engineered) that will selectively produce adequate analgesia and sedation without, at the same time, causing unwanted adverse effects. Furthermore, suitable neurostimulatory or neuroinhibitive methods involving the central nervous system are being sought that can amplify the analgesic action of opioids. In the search for antinociceptive agents as efficacious as currently available opioids, but without their troublesome adverse effects, the endogenous opioids, such as the endomorphins, are being examined as offering possible solutions to the adverse effect problem.

1. Introduction

Cancer pain is heterogeneous. Its nature depends on many factors, including the type of cancer, the disease location, the stage of the disease, and the patient's pain tolerance. In their classic book, *The Challenge of Pain*, Melzack and Wall [1] have pointed out that, compared with other kinds of pain, cancer pain is a special case.

> "… cancer does not induce the immune reactions which reject grafts. Furthermore, it does not even produce inflammation as a primary reaction.… A lung cancer may grow silently to the size of a grapefruit before any disorder is noticed.… What then, is the cause of pain if this silent enemy can infiltrate without disturbance? The answer is very largely mechanical.… In abdominal cancer pains, by far the commonest cause is mechanical obstruction of one or another of the viscera followed by dilation above the block … producing intense (painful) muscle contractions. On occasion, the tumor may have directly painful effects by expanding and increasing the pressure on sensitive structures—such as a bone tumor.…"

Cancer-induced pain is usually described under 3 headings: acute pain, chronic pain, and breakthrough pain (BTP). Acute pain, for example, may result from the pathologic

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fractures that occur when tumors invade bone. Although some of these fractures are initially painless, others may give rise to acute painful inflammation. One form of chronic pain may occur when cancers directly invade nerves causing severe neuropathic pain. Among patients with chronic, persistent cancer pain controlled by around-the-clock analgesics, there is a high prevalence of superimposed BTP —often precipitated by physical activity. It has been reported that more than 80% of patients with advanced, metastatic cancer experience BTP [2]. Breakthrough pain characteristically reaches peak intensity within a matter of minutes, requiring treatment with a rapidly acting, potent opioid.

When treating cancer pain, physicians have to select the analgesic best suited to the patient's particular clinical problem. What is needed is a medication—usually an opioid—that is sufficiently potent and prolonged in action to relieve the pain and keep it at bay for an appropriate period. To minimize the occurrence of damaging adverse effects, it is extremely important to assess the drug's safety profile in light of the patient's age, ethnic background, and overall medical condition. To enhance individualization of treatment, the physician needs answers to a number of questions; for example: How severe is the pain and how is the patient reacting to it? Are there preexisting medical or surgical problems that may be differentially exacerbated by certain opioids? Is the patient depressed or anxious? What other medications is the patient taking—antidepressants, sedatives, or tranquilizers? Does the patient have a history of seizure disorder or mental illness? Can the patient profit from certain ancillary or adjunctive treatments that may reduce the pain burden? Is there any reason to select a particular route (eg, oral, subcutaneous, transdermal, transmucosal, intrathecal) for administration of the analgesic?

Because of the complexities involved in treating severe cancer pain, the attending physician will often find it helpful to consult with a pain specialist, if one is available. The proliferation of clinics in pain control attests to the increased use of specialist-run pain services in both in- and outpatient settings.

2. Prevalence of pain in cancer patients

The onset of cancer is usually not heralded by pain. This is one reason why so many cancers are well advanced at the time of diagnosis. Not surprisingly, prevalence of pain increases as the disease progresses. The presence or development of comorbidities may complicate the pain picture. Moreover, pain prevalence is affected by type of neoplasm. For example, in their early stages, lymphomas and leukemias are less likely to be associated with pain than bone cancer or pancreatic cancer. After a cancer has spread, the pain it generates is no longer limited to one area; it is frequently experienced in 2 or more different parts of the body [3,4]. One survey found 2 or more distinct pain complaints in 81% of patients with advanced cancer. Thirty-four percent of these patients reported more than 3 different types of pain [5].

Overall, pain has been reported to occur in about 50% of cancer patients, regardless of the stage of the disease. More than 70% (and perhaps up to 90%) of patients with advanced cancer experience severe pain [3,4].

Cancer occurs most commonly in elderly people. In the United Kingdom, 74% of cancer cases are diagnosed in individuals at least 60 years old; and more than a third of cases occur in people aged at least 75 years [6]. In the United States, in 2007, 11.7 million men and women of all ages suffered from some form of invasive cancer. Of that total, 70% were at least 60 years of age [7]. From such data, it is possible to estimate that, at some point in the course of their illness, as many as 8.2 million US residents who currently suffer from invasive cancer will have pain sufficiently severe and persistent to require chronic opioid treatment. Of this number 5.7 million will be at least 60 years old.

Tumors that have spread to bone are the most common cause of cancer pain. Of patients with bone metastases, 60% to 80% experience pain because of the increased number of microfractures not seen on conventional x-rays. Tumors that infiltrate nerves and obstruct hollow viscera are common causes of severe cancer pain [3]. Obstruction in cancer can frequently be relieved by stenting. Nerve infiltration is more of a problem because tumor cells can travel along nerve sheaths and so can be difficult to localize, even with magnetic resonance imaging or positron emission tomographic scanning.

3. Opioids for treatment of cancer pain

At present, opioids are the most effective analgesics available for treatment of moderate and severe cancer pain. Over the years, a veritable arsenal of opioid compounds with a wide range of chemical, physiologic, and pharmacokinetic properties has become available for use in different pain situations. Certain attributes of 6 of the most commonly used opioid analgesics are listed in Table 1, together with the different routes of administration that have been used for the delivery of these compounds to patients under varying cancer pain circumstances. Such an array of choices enhances the physician's ability to individualize therapy.

4. Nonpharmacologic treatment of cancer pain

It is increasingly recognized that the perception of pain undergoes substantial modulation by a number of cortical mechanisms. There is evidence that the brain network for chronic pain perception may be, to some extent, distinct from that for acute pain. Chronic pain engages and interacts with brain regions that also process cognitive and emotional responses, suggesting that the eliciting of such responses may be among the features that distinguish chronic from acute pain [8]. According to Apkarian et al [8], the sensory system that generates pain arises from primary peripheral afferents that transmit pain messages that terminate in multiple brain areas. Thus, the experience of pain is subject to modulation

Table 1
Routes of administration and certain attributes of commonly used opioid analgesic medications

Commonly used opioid analgesic medications	Potency vis-a-vis morphine	Rapidity of action	Duration of action	Addiction potential[a]	Routes of administration (list incomplete)
Morphine (natural), standard against which all other opioids are tested	1 (benchmark level)	Plasma levels peak ~20 min after IM or SC injection	Elimination half-life ~120 min	Benchmark (high addiction potential)	PO, IM, SC, IV, IT
Oxycodone (semisynthetic), less sedating than morphine	1.5-2 (taken PO) ~1.5 (by injection)	Plasma levels peak ~60 min after conventional form is taken PO.	There are large interindividual variations in rate of metabolism among patients.	Fairly high without morphine's immediate euphoric effect.	PO, IM, IV,SC, IN, PR
Buprenorphine (semisynthetic), also used for detoxification in dependence treatment	25-30	Not given PO. (high first pass liver metabolism)	Mean elimination half- life is 37 h	Withdrawal is usually mild after short-term use.	IM, IV, SL,TD
Fentanyl (synthetic), often 1st choice for cancer pain	~100	Not given PO. (high first pass liver metabolism)	Transdermal patches can allow 48-72 h pain relief.	Addictive effect depends on duration of use.	TD, BU, IV (IV for painful procedures) IN, INH
Hydromorphone (semisynthetic morphine derivative)	8-10	Somewhat faster acting than morphine	Relatively short duration of action	Somewhat less than morphine	PO, IM, SC, POSRP, HPI, SL, BU, INH, NS, TD, IOP
Methadone (synthetic), usually given PO in racemic form	~3-5	Full analgesic effects not attained until 3-5 d of dosing.	Mean elimination half-life is 22 h. Pain relief lasts ~4-8 h.	Narcotic "rush" is rare. With slow detox, withdrawal is minimal.	PO, SL, drinkable form

The information in this table is for background purposes only and is not to be used in patient management. Sources: Physicians Desk Reference, 2010; http://www.drugs.com. PO indicates by mouth; SC, subcutaneous; IM, intramuscular; IV, intravenous; POSRP, PO sustained release preparation; HPI, hydromorphone polymer implant; SL, sublingual; BU, buccal; INH, inhalation of nebulized drug; IN, intranasal; TD, transdermal (patch); IOP, implantable osmotic pump; IT, intrathecal; PR, per rectum.

[a] Addiction is rare when a drug is used for pain relief.

by a number of influences, including emotional and cognitive responses to pain, and genetic factors affecting both sensory vulnerability to pain and the way pain is interpreted. As more investigative attention is given to these modulatory processes, the information that emerges will be (and is being) increasingly applied in the management of chronic pain.

The fact that a number of nonpharmacologic measures have been found to be effective as adjuncts to opioid treatment in the relief of cancer pain is supportive of the broad concept that pain perception in the human brain is subject to substantial modulation by "mind-body" interventions.

The National Institute of Health's National Cancer Institute has listed a series of nonpharmacologic agencies that may have utility as adjuncts to the treatment of cancer pain [9]. These measures include acupuncture [10], biofeedback [11], virtual reality programming ("distraction") [12], hypnosis [13], imagery (focused daydreaming), massage, meditation and relaxation (a number of relaxation techniques are available) [9], listening to soothing music [14], religious counseling [9], meditation, and cognitive-behavioral therapy [15].

In the treatment of cancer pain, the art of practicing medicine can be very useful.

5. The 3-step approach to cancer pain management

With respect to analgesics, the World Health Organization has developed a 3-step "analgesic ladder" [16] to guide management of cancer pain, based on the pain's severity, estimated by use of a 1 to 10 numeric rating scale (Table 2). If the pain falls within the 1 to 4 range, it is considered "mild." The WHO recommends that, when possible, acetaminophen and nonsteroidal anti-inflammatory agents (NSAIDs) may be used initially to control mild cancer pain. Contrary to popular belief, these agents are not always benign; and patients—especially elderly patients—who use them need to be monitored carefully for adverse effects, particularly in patients with liver, gastrointestinal (GI) disease, or renal failure. Acetaminophen, for example, is capable of producing severe liver damage, particularly if the amount taken exceeds the maximum recommended daily

Table 2
The WHO 3-step guide for treatment of pain in patients with cancer [11]

Steps and pain intensity (scale: 1-10)	Recommended medications
1. Mild pain (1-4)	Acetaminophen, NSAIDS (± adjuvants)
2. Moderate pain (5-6)	Hydrocodone, oxycodone, tramadol (± nonopioid analgesics) (± adjuvants)
3. Severe pain (7-10)	Hydromorphone, methadone, fentanyl, oxycodone (± nonopioid analgesics) (± adjuvants)

The term *adjuvants* refers to medications that are coadministered to manage an adverse effect of an opioid or to adjuvant analgesics that are added to enhance analgesia, such as steroids for pain caused by bone metastases. Adjuvants may also include drugs such as anticonvulsants for neuropathic pain.

dose of 4000 mg for adults [17]. Nonsteroidal anti-inflammatory drugs can damage the mucosal lining of the GI tract, particularly the stomach and upper small intestine. The risk of serious GI bleeding in NSAIDs users is significantly increased among patients who are being treated with anticoagulants or corticosteroids (like prednisone), regularly consume significant quantities of alcohol, or have a history of peptic ulcer.

When cancer pain lasts or increases beyond the mild stage, it enters the "moderate" 5 to 6 category. At that point, the prescription may be changed to step 2 or step 3 medications. Indeed, if the presenting pain is sufficiently severe, the prescribing physician may skip step 1 medications. Step 2 medications include hydrocodone, oxycodone, and tramadol.

When cancer pain reaches the 7 to 10 category of severity, step 3 medications are appropriate. They include hydromorphone, methadone, fentanyl, and oxycodone.

6. Some considerations governing selection of an opioid for analgesic use

According to a 2008 International Expert Panel consensus statement on opioids and management of chronic severe pain in the elderly [18], the 6 most commonly used WHO step 3 opioids are morphine, oxycodone, buprenorphine, fentanyl, hydromorphone, and methadone (Table 1). In the Consensus Statement, the criteria set forth for selecting analgesics for the treatment of pain in older patients included (1) overall efficacy, (2) overall adverse effect profile, (3) onset of action, (4) drug interactions, (5) abuse potential, (6) severity and type of pain, and (7) cost and availability of the drug, including availability of preparations for transdermal, sublingual, and other non-GI routes of delivery.

When opioids are taken by mouth, a substantial fraction of the administered medication (up to 50% in the case of morphine) may be inactivated during its initial passage through the liver. This "first pass" effect makes the oral route relatively inefficient, although it is often more convenient for the patient and the nursing staff. For acute, severe cancer pain, parenteral administration of opioid analgesics may be preferred because it ordinarily provides enhanced dose control together with more rapid pain relief.

As Table 1 shows, when today's physicians are faced with a difficult case of cancer pain, they must choose—from an array of options—the safest and most effective opioid analgesic and the most appropriate drug delivery system. Such decisions require considerable knowledge about opioids and experience with their use in a variety of clinical situations. If the patient is suffering from intractable pain and other routes of administration have not worked well, intrathecal opioids may be considered. Its use, however, requires special expertise. The therapeutic action of intrathecal administration lasts longer and may be associated with a reduced occurrence of systemic adverse effects [19].

In patients who are no longer responsive to opioids for moderate pain, sustained-release oral morphine, transdermal fentanyl, and oral methadone are options (among many others) that have been reported to be comparably effective [20].

7. Treatment of BTP

There is a need for a rapidly acting, powerful "rescue" analgesic for treatment of BTP. Intravenously given morphine has been used for this purpose with reported success [21]. However, fentanyl has features that appear to make it preferable for treatment of BTP. Fentanyl's potency is about 100 times that of morphine, and its analgesic activity is of relatively short duration after it is administered intravenously or subcutaneously. It is less constipating than morphine. Because of its low molecular weight and lipid solubility, fentanyl seems well suited for delivery via a transmucosal or an intranasal system. When fentanyl is administered as a buccal tablet, absorption of the drug through the buccal mucosa is rapid, providing significant pain relief within 30 minutes [22]. In addition, long-acting (72 hours) skin patches may be tried. However, their use in elderly patients can frequently cause cognitive impairment. On the other hand, intranasal fentanyl spray can produce a substantial reduction of BTP as soon as 15 minutes after it is taken [23]. Both routes of administration seem equally well tolerated; however, intranasal fentanyl spray may become the treatment of choice because of its more rapid action.

8. Opioid receptors and the search for the ideal analgesic

Research conducted in many laboratories since the 1960s has established that there are (at present) 4 important G-protein–coupled opioid receptors, known as μ, δ, κ, and *nociceptin receptor*, respectively. Many other receptors and putative receptors are under active investigation. The μ, κ, and δ receptors are composed of 3, 3, and 2 subtypes, respectively (μ_1, μ_2, and μ_3; κ_1, κ_2, and κ_3; and δ_1 and δ_2). These receptors are located in various parts of the brain, in the spinal cord, and also (in the case of the μ-opioid receptors) in the GI tract. The pharmacodynamic response to any given opioid depends on the nature of the receptor to which the opioid binds, its affinity for the receptor, and whether it acts as an agonist or (in the case of naloxone and naltrexone) an antagonist. Morphine, for example, binds strongly to and activates the μ-opioid receptors [24,25]. The physiologic results include analgesia, sedation, euphoria, respiratory depression, pruritus, and reduced GI motility (causing constipation and, sometimes, gastric stasis) that may augment the nausea and vomiting that result from morphine's direct stimulation of the vomiting center.

Apparently, morphine also binds to κ- and δ-opiate receptors, causing marked miosis (pinpoint pupils), spinal analgesia, and psychotomimetic effects [26,27].

The existence of various opiate receptor subtypes, each with its own repertoire of responses, has given rise to the hope (still unrealized) that it might be possible to identify or design an opioid that would bind selectively to a receptor subtype that specifically produces adequate analgesia and sedation, without, at the same time, causing such unwanted adverse effects as respiratory depression, cognitive impairment, constipation, pruritus, physical dependence, and analgesic tolerance.

As pointed out by Millan [28] and O'Callaghan and Miller (this issue of *Metabolism*), the dorsal horn of the spinal cord is under the influence of at least several descending mechanisms capable of enhancing or inhibiting the passage of pain messages to higher centers. Discovery of one or more new drugs capable of interfering with the descending facilitation of pain transmission at the spinal horn level could result in an important advance in cancer pain control.

9. Endogenous opioids

Endogenous opioid peptides are opioids produced naturally in the body. They include endorphins, enkephalins, dynorphins, and endomorphins. β-Endorphin is expressed in cells in the arcuate nucleus of the hypothalamus and in the brainstem. It acts via μ-opioid receptors and influences appetite and sexual behavior. Enkephalin is widely distributed throughout the brain and acts through μ- and δ-opioid receptors. Dynorphin acts via κ-opioid receptors and is found in the spinal cord and in many parts of the brain, including the hypothalamus. The endomorphins (endomorphin-1 and endomorphin-2) bind strongly and preferentially to μ-opioid receptors, activating G-proteins, with potent analgesic and GI effects [29,30].

To a varying degree, endorphins, as a class, resemble the opiate drugs in their ability to produce analgesia and a feeling of euphoria. Fortunately, they do not seem to generate the kinds of adverse effects commonly associated with administration of opioid medications.

In the search for antinociceptive agents that are as effective as currently available opioids but lack their troublesome adverse effects, the endogenous opioids (or congeners thereof) have been looked at as offering possible solutions to the adverse effect problem. As one example, enkephalinase inhibitors have been studied as potential agents for pain management [31]. Popik et al [32] have reported that human opiorphin peptide, an endogenous enkephalinase inhibitor, displays promising antinociceptive action in several pain models. However, its opioid adverse effect profile remains to be more fully characterized.

From the ever-increasing number of publications on the subject, it is evident that efforts are accelerating to discover new analgesics that retain the antinociceptive potency of opioid medications while eliminating or greatly reducing their adverse effects [33]. As part of the attempt to solve this problem, further study of the opioid receptors and the endogenous opioids should continue to yield useful information.

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