Opioids in Cancer Pain: Common Dosing Errors

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Many individuals with advanced malignancy continue to suffer from pain and, consequently, impaired quality of life. The clinical scenarios in advanced cancer pain are complex, and successful management may require a more sophisticated and individualized approach than suggested by the World Health Organization guidelines. In patients referred to the Harry R. Horvitz Center for Palliative Medicine in Cleveland, numerous commonly occurring errors in opioid use have been noted. This article describes these errors and offers strategies with which to improve outcomes for patients suffering with cancer pain.

ABSTRACT: Many individuals with advanced malignancy continue to suffer from pain and, consequently, impaired quality of life. The clinical scenarios in advanced cancer pain are complex, and successful management may require a more sophisticated and individualized approach than suggested by the World Health Organization guidelines. In patients referred to the Harry R. Horvitz Center for Palliative Medicine in Cleveland, numerous commonly occurring errors in opioid use have been noted. This article describes these errors and offers strategies with which to improve outcomes for patients suffering with cancer pain.

The classic approach to analgesia in cancer patients is both opioid and adjuvant medication prescribed in a stepladder fashion, as established by the World Health Organization (WHO). Since its inception, these guidelines have been validated and are now applied worldwide.[1] Given that over 80% of patients living with advanced cancer experience pain, it is one of the most common and severe problems in this population.[2,3] Oncologists must therefore be familiar with the effective use of analgesics. Many individuals with advanced malignant disease continue to suffer with pain and, consequently, impaired quality of life.[4-6] Why do those who complain of pain to their physician and receive treatment still suffer? In reviewing the literature and observing physician management decisions in patients referred to us in a tertiary care hospital, we have noted numerous gaps between theory and practice.[7]

In practice, clinical scenarios involving pain in advanced cancer are complex and require more sophisticated individualized approaches than those addressed by the WHO guidelines. Proper opioid management takes into account the quality and severity of pain as well as the time course—whether pain is constant, incident, or breakthrough in nature. Medically sound strategies for initiating opioids are based on the pharmacokinetic and pharmacodynamic properties of these agents, in addition to general prescribing principles.

Finding the right opioid for an individual requires trial and error. Reassessment for response may identify problems with the current opioid regimen. Even with dose titration, an opioid may not control the pain or cause persistent adverse effects. Assuming a sufficient trial of the original regimen has been attempted, this may require rotation to a new opioid or a new route of administration. To rotate opioids effectively, the physician must have an understanding of equianalgesic dosing for different opioids and routes. Appropriate prescribing, coupled with frequent reassessment and rotation if necessary, will provide effective analgesia for most patients with advanced cancer pain.

In patients referred to us for the management of cancer pain, we have recognized several commonly occurring errors in opioid use prior to the referral. As reported here, these observations are based on collective and collaborative clinical experience at our dedicated palliative medicine inpatient unit, as well as the inpatient and outpatient consulting services. The errors may be grouped into three categories: (1) errors in strategy, (2) errors in titration, and (3) errors in conversion.

In this article, we describe these errors, why each may occur, and the consequences. In accordance with the basic principles of opioid management that guide our practice, we also offer strategies to avoid these errors and improve outcomes for patients suffering with cancer pain. Morphine sulfate is the opioid of first choice in our practice.[3] For illustrative purposes in this report, we will use
Strategic Errors

Error #1: Rescue or As-Needed Prescribing for Constant Pain

Given constant pain, it is appropriate to start regular repeated doses of opioids. It is inadequate to leave a patient on rescue, or as-needed (prn), dosing alone. If only rescue dosing is employed, patients will be continuously trying to catch up with their pain. As a result, life revolves around not only the pain but also frequent medication. Rescue dosing for continuous pain at 3- to 4-hour intervals will also disturb sleep, as individuals will awaken during the night with pain and to take medication.

• Correction—This situation first requires a careful assessment of the temporal pain patterns. A general rule is that continuous pain needs continuous analgesia. This may be accomplished with (1) oral sustained-release (SR) medications, (2) transdermal medication, (3) parenteral continuous infusion, or (4) oral immediate-release (IR) medications scheduled around-the-clock (ATC). The option of choice is an oral SR medication, which is easily prescribed in the outpatient setting.

If pain is severe, requiring rapid dose titration, then continuous parenteral (subcutaneous or intravenous) infusion—usually in the inpatient setting—is recommended to establish quick control. Although used less often since the development of SR opioids, regularly scheduled IR opioids are an alternative. A double-dose of the IR medication at bedtime is safe and can usually avoid the need to wake for dosing during sleep.

Error #2: Scheduled Prescribing Without Rescue Dosing

While continuous pain calls for ATC medication, pain levels vary. Breakthrough pain is an unpredictable exacerbation of baseline pain. Failure to identify breakthrough pain causes inappropriate management. Individuals not given IR rescue opioids to take as needed may have significant pain before their next scheduled ATC dose. They will mistakenly believe their SR medication is ineffective. In response, physicians may increase SR dosing, producing adverse effects such as delirium, nausea, and sedation. Patients may also use or be given SR opioids to take as needed but, given the delayed analgesic onset, find them ineffective.

• Correction—Always prescribe a prn rescue opioid dose when initiating SR opioid therapy. The rescue dose should be an IR preparation, usually the same opioid as the sustained-release drug. SR medications should never be dosed prn. If rescue medication is required more than four times in 24 hours, the SR dose may be increased in an effort to prevent the breakthrough pain. An example of this process follows.

Mr. T. is taking 60 mg of SR morphine sulfate every 12 hours. He has required eight 15-mg doses of IR morphine for breakthrough pain, with good relief and no side effects. Over 24 hours, he used an additional 120 mg of IR morphine. His SR dose is increased by 120 mg, for a new total daily SR morphine dose of 240 mg, or 120 mg every 12 hours. Because his rescue dose has been effective, it is not changed.

Error #3: Not Using Prophylactic Rescue Dosing for Incident Pain

Incident pain is brought about by a specific action or event, which may be voluntary (moving, walking, eating) or involuntary (cough, defecation). Specific identification of incident pain is important, as it limits activity and creates a high probability of suboptimal pain control. Incident pain will not be effectively managed by SR medications alone, and oral rescue doses may not take effect rapidly enough for adequate control.

• Correction—As incident pain, by definition, is usually predictable, it is more effective to give rescue dosing before a known precipitating event. The rescue dose should be enough to control the incident pain and may often be larger than that required for breakthrough pain. Parenteral administration is sometimes needed for quick action. Buccal fentanyl (Actiq) is an alternative in this situation.

Error #4: Use of Multiple Opioids and/or Formulations

We commonly encounter simultaneous use of both transdermal fentanyl (Duragesic) and SR morphine sulfate for continuous pain, and both IR oxycodone and IR morphine for breakthrough pain. That is, instead of titrating the initial SR opioid dose to pain relief, a second opioid was added. Multiple opioids complicate a regimen and risk confusing patients and caregivers. Usually neither
medication is being given at adequate doses.

• **Correction**—Only one extended-release opioid should be used and increased until either adequate pain control or toxicity occurs. Whenever possible, the same opioid should be used for the IR dosing (ie, SR and IR morphine sulfate or SR and IR oxycodone). If a new opioid is required—such as in the setting of unacceptable side effects—an equianalgesic dose of the new opioid is calculated. The original opioid is discontinued, and the new medication initiated and titrated until analgesia is achieved.

**Error #5: Not Prescribing Adjuvant Analgesics**

The WHO guidelines recommend the addition of adjuvant analgesics at each step on the ladder if needed to achieve adequate analgesia, yet this is often not done. Common adjuvants include nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, tricyclic antidepressants, anticonvulsants, corticosteroids, and antiarrhythmics. Adjuvants may be particularly helpful for neuropathic pain, which is often incompletely controlled with opioids alone.

• **Correction**—The appropriate use of adjuvant analgesics requires a careful pain assessment. Typically, NSAIDs or corticosteroids are used in bone pain and antidepressants or anticonvulsants in neuropathic pain. Whether opioids or nonopioids are used as the primary analgesic, an adjuvant medication may contribute to improved pain control. If opioid toxicity occurs with titration, the addition of an adjuvant medication may improve pain control enough to allow an opioid dose reduction and elimination of the unacceptable side effect.

**Titration Errors**

**Error #6: Insufficient Rescue Dose Titration**

During opioid titration, the ATC dose may be increased inappropriately instead of the rescue dose, or the ATC and rescue doses may be increased simultaneously. Careful assessment of the pain pattern is required before adjustment: How many breakthrough doses are required? As in the example above, frequent rescue dosing may warrant an increase in SR dose. However, one must also assess the efficacy of the rescue dose: How well does it relieve pain, and how long does the relief last?

• **Correction**—The rescue dose should be titrated to fully relieve intermittent pain, whether it is breakthrough pain or incident in nature. A percentage dose-response calculation is practical and quick. Some suggest that rescue doses should be a fixed percentage of the 24-hour daily dose. Although this may be appropriate for initiating rescue dosing, practical experience and recent studies with fentanyl suggest that the SR and rescue doses are often unrelated.[3,11]

The rescue dose that provides effective analgesia for the breakthrough pain without toxicity is the correct dose. If pain relief following a rescue dose is inadequate, that dose should be increased. Conversely, if oversedation occurs with the dose, it should be reduced.

**Error #7: Scheduled Dose Titration for Incident Pain**

Since incident pain is transient, increasing the SR dose to control it may result in toxicity. Those with incident pain caused by voluntary activity are often comfortable at rest. Just as the SR dose cannot manage incident pain, the rescue doses required for incident pain should not affect the SR dose.[13]

• **Correction**—Frequent rescue dosing for breakthrough pain may necessitate an increase in SR dose. Careful assessment helps differentiate incident from breakthrough pain (recognizing that an individual may have both). Incident pain rescue doses should not be used to calculate SR dose requirements. For example:

> Mr. D. takes SR morphine sulfate, 60 mg every 12 hours, with good control of baseline pain. He has incident pain when he stands for more than a few minutes. His incident pain is controlled with 30 mg of IR morphine premedication, with usually four rescue doses a day. Despite the additional 120 mg daily, an increase in SR dose would be inappropriate in this situation and might cause toxicity due to overmedication at times when there is no incident pain.

**Error #8: Pharmacologically Incorrect Dosing**

Sustained-release opioids are often prescribed at inappropriate intervals—ie, every 6 or 8 hours. The most commonly used SR opioids have an analgesic duration of 12 hours. Other oral products continue to be effective for up to 24 hours, and transdermal fentanyl lasts up to 72 hours.[14,15] Just
as SR opioids may be dosed too frequently, rescue doses may be prescribed too infrequently. The duration of action for most immediate-release opioids dosed orally is up to 4 hours.\[14] Parenteral duration of action is often shorter. The common practice of 4- to 6-hour or simply 6-hour intervals is therefore inappropriate.

The consequences of this error are numerous. Prescribing SR opioids more often than every 12 hours complicates compliance and increases the cost of care. The schedules for appropriate 8-hour dosing require early morning awakening and interfere with sleep for patients and/or caregivers. Overly prolonged intervals for breakthrough medication leave the patient in pain, watching the clock until the next dose is due, while pain may escalate to a level no longer effectively relieved by the prescribed dose.

**Correction**—SR morphine sulfate every 12 hours is usually adequate. If pain control is inadequate, then careful reassessment is required. Is the pain consistently uncontrolled? Then a change in dose rather than a change in interval is needed. Does the pain return consistently before the next dose of SR medication? Then end-of-dose failure is the problem. This occurs when analgesia falls below that needed for relief before the next dose is due. Breakthrough pain will then occur predictably in the hours before each scheduled opioid dose.

A precise history eliciting the time of opioid dose and the relative time to onset of pain is crucial. Management requires either an increase in the scheduled dose (preferred) or reducing the dosing interval (ie, from 12 to 8 hours). Only a minority of patients will require more frequent dosing.\[15,16\] Intervals for SR opioids less than every 8 hours are inappropriate. An example of a common scenario follows.

**Mr. K.** was transferred to our hospital unit on 90-mg SR morphine sulfate dosed every 8 hours. When asked how he came to be on an every-8-hour schedule, he states that he has always been on this regimen. Since pain was controlled and he had no history of end-of-dose failure, a trial of twice daily dosing was prescribed, and pain continued to be controlled.

**Error #9: Changing More Than One Drug at a Time**

Only one change to an analgesic regimen (drug, dose, route, schedule) should be made at a time. For example, we were consulted on a patient who was started on morphine, gabapentin (Neurontin), and celecoxib (Celebrex) at the same time. While analgesia may be achieved, to which drug is it attributable? If it was the adjuvants, the patient may now be on excessive opioids and subject to associated risks. If it was the opioid, then the patient is now taking additional analgesics unnecessarily. If side effects occur, how will we determine which medication is responsible? The same problem can occur when decreasing opioid doses. If both the SR and rescue doses are reduced simultaneously and the dose reduction is not tolerated, a person may have uncontrolled pain.

**Correction**—Change one medication at a time so that subsequent events can be attributed correctly. Evaluate the response and tolerance to that medication, including appropriate titration, before adding a second. If titrating down, then the SR dose should be decreased first, leaving rescue doses unchanged (assuming there is no toxicity with the current rescue dose).

**Conversion Errors**

**Error #10: Incorrectly Calculating Equianalgesic Doses**

Individuals on chronic opioids often return from a surgical procedure with acute pain complicating their preexisting pain. All too commonly, patients actually receive lower doses of opioids in the postoperative period than preoperatively, and are therefore not comfortable. Another common scenario involves a patient who is vomiting and unable to take oral medications; the substituted parenteral dose may not be equivalent to the prior oral opioid dose.

**Correction**—There is no fixed conversion ratio that holds true for all situations, but physicians should become familiar with oral/parenteral ratios and equianalgesic conversions for common opioids. Conversion tables are available, and are generally accepted as a starting point.\[17,18\] As equianalgesic tables are only general guidelines, the exact dose is determined individually. We rotate at a decrease of about 30% from the calculated dose, to account for side effects.\[19\] If pain control is incomplete, we rotate to 100% of the calculated equianalgesic dose. Frequent reassessment for response and side effects with appropriate opioid titration proceeds until pain control occurs. For example:

**Mr. R.** is on 75 mg of SR morphine every 12 hours. He is admitted to the hospital for intractable
vomiting and needs an opioid route change. The parenteral morphine sulfate dose is equianalgesic to one-third the oral dose. For parenteral conversion, first calculate the total daily oral morphine dose (150 mg). One-third of this dose is 50 mg, which is the total daily parenteral morphine dose. Divide this number by 24 hours to derive the hourly morphine infusion rate (approximately 2 mg/h) to be delivered either intravenously or subcutaneously.

**Error #11: Inadequate Follow-up** With the desire for early hospital discharge, physicians may convert inpatients to oral opioids on the day of discharge without confirming the efficacy of the regimen. This may result in either readmission or a patient who remains at home suffering with continuing pain, defeating the purpose of the original admission. In the outpatient setting, a prescription for a new medication may be given with no follow-up planned for weeks.

**Correction**—When a new medication is initiated for pain control in the outpatient setting, the response and toxicity should be assessed within a week. Earlier phone contact is appropriate when possible. Frequent follow-up allows the careful assessment and titration necessary to achieve pain control with minimal toxicity. Since equianalgesic calculations are only guidelines, patients should be observed for 24 hours after conversion from a parenteral to an oral regimen. This will allow assessment of the efficacy of the conversion and the frequency of rescue dosing. Further titration
may be required prior to discharge.

**Discussion**

Effective pain management requires a thorough history and frequent reassessment. Strategies for opioid dosing, rotation, and adding adjuvant medications can be implemented and redefined with subsequent patient visits. There is no shortcut. Management of cancer pain is partly trial and error, with close supervision by the physician. Acceptance of this idea is perhaps the first step in avoiding the errors presented. Attention to good prescribing principles and some fundamental knowledge of pharmacokinetics, pharmacodynamics, and side effects will obviate many errors. Identifying and exploring problems in cancer pain assessment and management clarifies obstacles in improving pain control and quality of life. The reasons for errors are manifold and often reflect a disconnect of knowledge from clinical practice. Both physicians and patients tend to be uncomfortable with opioid medications, even with established guidelines such as those outlined by the WHO. We have presented some common errors and corrective suggestions as an essential first step from theoretical to actual pain control. Ineffective analgesia is not a failure, but an opportunity from which practical understanding of clinical strategies and implementation can begin.

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