

Opioid Rotation in the Management of Refractory Cancer Pain

By Rose Anne Indelicato and Russell K. Portenoy

HERE'S THE CASE: A 59-year-old woman notes worsening bone pain caused by a non-small-cell lung cancer metastatic to the ribs and spine. She has been treated with radiation and chemotherapy. During the past 3 weeks, she developed worsening posterior thoracic pain at the site of a previously irradiated rib lesion. A recent computed tomography scan of the chest showed that the mass was increasing in volume and extending into the chest itself. A surgical option for local control of this lesion was considered, but it was rejected by the patient.

Before her pain increased, it had been adequately controlled for 4 months with a combination of an extended-release morphine formulation (200 mg taken twice daily) supplemented with a short-acting morphine formulation (30 mg every 2 hours as needed) for episodes of breakthrough pain. Her use of the short-acting morphine, or rescue dose, had increased to three times per day during the past week, but her pain was still not controlled.

Two days ago, the patient called and was told to increase the morphine dose and add ibuprofen. She is now taking 200 mg of morphine every 8 hours and still has required about three extra doses of the short-acting morphine per day. Despite the increase in her dose, her pain continues to be uncontrolled and she is experiencing sedation and nausea.

The patient verbalizes her frustration and asks, "Doctor, isn't there something you can give me for this pain that won't make me feel so sick?"

THE PROBLEM

Chronic opioid therapy is the mainstay treatment for moderate to severe cancer-related pain. Most patients can be effectively managed if well-accepted guidelines are systematically applied.¹ One of the most important of these guidelines calls for individualization of the opioid dose through a process of gradual dose titration. Specifically, the dose should be increased in steps (typically by 33% to

100%, depending on the circumstances) until either adequate analgesia is attained or intolerable and unmanageable side effects occur.

Opioid responsiveness refers to the likelihood that a favorable balance between pain relief and side effects can be achieved during dose titration.² Ten percent to 30% of patients are like the patient in this case and demonstrate poor responsiveness to an opioid during routine administration. Poor responsiveness is a complex phenomenon that may be related to one or more of a diverse group of factors, including comorbid medical disorders that predispose to toxicity, a pain pathophysiology associated with relatively limited analgesic response, and pharmacologic effects such as the accumulation of active metabolites caused by dehydration or renal insufficiency.³⁻⁵

If gradual dose titration yields treatment-limiting toxicity, an alternative therapeutic strategy is needed. Potential strategies for addressing poor opioid responsiveness include the following:

- The use of a more aggressive or innovative therapy for side effects, such as coadministration of a psychostimulant for opioid-related somnolence.
- The use of a pharmacologic intervention that may reduce the systemic opioid requirement, such as coadministration of a nonopioid or adjuvant analgesic.
- The use of intraspinal therapy to reduce the systemic opioid requirement.
- The use of a nonpharmacologic intervention (such as transcutaneous nerve stimulation, a cognitive approach, neural blockade, or a complementary therapy) that may reduce the systemic opioid requirement.
- A switch to another opioid in the hope of achieving a more favorable balance between analgesia and side effects.

OPIOID ROTATION

The switch from one opioid to another when treatment-limiting toxicity establishes poor responsiveness has become known as opioid rotation. The approach is based on the clinical observation that intraindividual response varies remarkably from opioid to opioid and that a change to an alternative drug may yield a far better balance between analgesia and side effects.⁶⁻⁸

From the Department of Pain Medicine and Palliative Care, Beth Israel Medical Center, New York, NY.

Address reprint requests to Russell K. Portenoy, MD, Department of Pain Medicine and Palliative Care, Beth Israel Medical Center, First Ave at 16th St, New York, NY 10003; email: rportenoy@bethisraelny.org.

© 2001 by American Society of Clinical Oncology.

0732-183X/01/2001-348/\$20.00

Table 1. Opioid Analgesics Used for Severe Cancer Pain

Morphine-Like Agonists	Equianalgesic Dose*	Half-Life (hours)	Comments
Morphine	10 im 30 po†	2-3 2-3	Constipation, nausea, sedation most common side effects; respiratory depression rare in cancer patients; standard for comparison for opioids; multiple formulations available
Hydromorphone‡	1.5 im 7.5 po	2-3 2-3	Side effects similar to morphine
Oxycodone	20 po§	2-3	Side effects similar to morphine
Levorphanol	2 im 4 po	12-15	Side effects similar to morphine; with long half-life, accumulation occurs after beginning treatment or increasing the dose
Methadone	10 im 20 po	12-> 150	Side effects similar to morphine; racemic mixture contains d-isomer, an NMDA antagonist that is probably the cause of potency greater than indicated by the equianalgesic table; reduce equianalgesic dose by 75% to 90% and be aware that long half-life can lead to delayed toxicity after beginning treatment or increasing the dose
Fentanyl (transdermal)	—	16-24	Equianalgesic doses available in package insert; based on clinical experience, the 100 µg/h transdermal system is roughly equianalgesic to intravenous morphine 4 mg/h

NOTE. Adapted from Portenoy.²

Abbreviations: im, intramuscular; po, oral.

*Dose that provides analgesia equivalent to 10 mg of intramuscular morphine. These ratios are useful guides when switching drugs or routes of administration (see text). In clinical practice, the potency of the intramuscular route is considered to be identical to the intravenous and subcutaneous routes.

†Extensive survey data suggest that the relative potency of intramuscular:oral morphine, which has been shown to be 1:6 in an acute dosing study, is 1:2-3 with chronic dosing; 30 mg was chosen for simplicity.

‡Survey data suggest that the relative potency of hydromorphone intramuscular:oral is 5:1 in an acute dosing setting but may change to 3.7:1 with chronic dosing.¹⁰

§Some data suggest 20 to 30 mg; 20 mg was chosen for simplicity.

Guidelines for opioid rotation are intended to reduce the risk of relative overdosing or underdosing as one opioid is discontinued and another is administered.⁹ These guidelines require a working knowledge of an equianalgesic dose table¹⁰ (Table 1).

The equianalgesic dose table provides evidence-based values for the relative potencies among different opioid drugs and routes of administration. The values were derived from well-controlled single-dose assays conducted in cancer populations with limited opioid exposure.¹¹ The dose table simplifies comparisons by describing all potencies relative to a standard, which is defined as morphine 10 mg parenterally.

The equianalgesic dose table provides only a broad guide for dose selection when a switch from one opioid to another is contemplated.^{9,12} In most cases, the calculated dose equivalent of a new drug must be reduced to ensure safety (Table 2). Based on clinical experience, the starting point for dose reduction from the calculated equianalgesic dose is 25% to 50%. There are several reasons for this. First, there is a potential for incomplete cross-tolerance between opioid drugs. This would lead to effects (including adverse effects)

that would be greater than expected when a switch to a new drug is made. Second, there appears to be large interindividual variability in the relative potencies among opioids. As a result, the ratios listed in the equianalgesic table may be more or less than the ratio that would be found if a single-dose study was performed in the individual patient.

Table 2. Dose Conversion Guideline

- Calculate the equianalgesic dose of the new opioid based on the equianalgesic table.
- If switching to any opioid other than methadone or fentanyl, decrease the equianalgesic dose by 25% to 50%.
- If switching to methadone, reduce the dose by 75% to 90%.
- If switching to transdermal fentanyl, do not reduce the equianalgesic dose.
- Consider further changes in the adjusted equianalgesic dose based on medical condition and pain.
 - If the patient is elderly or has significant cardiopulmonary, hepatic or renal disease, consider further dose reduction.
 - If the patient has severe pain, consider a lesser dose reduction.
- Calculate a rescue dose as 5% to 15% of the total daily opioid dose and administer at an appropriate interval.
- Reassess and titrate the new opioids.

Third, there is a need to adjust treatment for conditions that increase opioid risk, such as advanced age and medical comorbidities. Fourth, it is likely that the relative potencies derived from single-dose assays differ from those that would be found if repeated-dose assays were done. The published values, therefore, can only approximate the clinical situation.

Both clinical experience and survey data suggest that there are two exceptions to the guideline that dose reduction from the calculated equianalgesic dose should start at 25% to 50%. The first exception occurs with conversion to a transdermal fentanyl system (TFS). In the development of this formulation, conversion guidelines were developed that incorporated a safety factor, obviating the need for additional dose reductions in most patients.

The second exception occurs with conversion to methadone. A larger reduction in the calculated equianalgesic dose, specifically 75% to 90%, is justified by data that demonstrate a much greater potency than expected when switching to methadone from another pure mu agonist, such as morphine.¹³⁻¹⁵ Indeed, some data indicate that the potency of methadone following a switch from another mu agonist is dependent on the dose of the prior drug^{14,15}; a higher dose, such as 500 mg of morphine or greater, requires a larger dose reduction than a smaller dose.

This unanticipated potency of methadone is believed to be related to the d-isomer, which in the United States represents 50% of the commercially available racemic mixture. This isomer blocks the N-methyl-D-aspartate receptor and, as a result, may yield independent analgesic effects and partially reverse opioid tolerance.^{16,17}

Once the calculated equianalgesic dose is reduced by 25% to 50% (75% to 90% in the case of methadone), further dose adjustments might be considered based on medical condition and the degree of unrelieved pain. For patients who are elderly or have significant cardiopulmonary, hepatic, or renal disease, the new opioid may be reduced by more than 50%. In contrast, if a patient reports severe pain, the new opioid dosage may be administered at the calculated equianalgesic dosage, foregoing the usual percentage reduction.

NOW BACK TO THE CASE

The patient is experiencing inadequate pain relief and intolerable side effects related to the increase in her morphine dosage. The decision is made to rotate to an alternative long-acting opioid, specifically an extended-release oxycodone formulation. Because the patient is reporting severe pain and does not have major organ involvement, the decision is made to order the equianalgesic dose without the usual reduction in the calculated dose.

Here's How the Switch Was Done

1. The 24-hour dose of previous opioid (including the fixed schedule dose and the supplemental doses taken as needed) was calculated.

Long-acting (200 mg every 8 hours) + immediate-release morphine (3 doses of 30 mg)

Total for 24 hours = 690 mg orally (po)

2. The oral dosage of morphine is converted to the oral dosage of oxycodone, using the equianalgesic table.

Morphine 30 mg po = oxycodone 20 mg po

Morphine 690 mg po = oxycodone 460 mg po

3. The 24-hour total is converted into a divided fixed schedule.

Oxycodone 460 mg/24 hours = extended release oxycodone 230 mg every 12 hours. This is approximated as a dose of three 80-mg tablets every 12 hours.

Selection of a Rescue Dose

The patient requires a fixed dosing schedule of a long-acting opioid to treat continuous bone pain. In addition, an as-needed rescue dose of short-acting opioid should be ordered to provide relief of intermittent breakthrough pain. The usual dose for rescue medication ranges between 5% and 15% of the total daily dose. The interval should be long enough to observe the full effect of each dosage. In the case of oral opioids, a schedule of every 2 hours is appropriate. In this case, oxycodone is chosen as the rescue drug.

To Calculate the Rescue Dosage

1. The 24-hour total dose is calculated.

Extended-release oxycodone 230 mg every 12 hours = 460 mg every 24 hours

$460 \text{ mg} \times 5\% = 23 \text{ mg}$

$460 \text{ mg} \times 10\% = 46 \text{ mg}$

$460 \text{ mg} \times 15\% = 69 \text{ mg}$

2. A dose and an interval appropriate for the specific short-acting opioid is chosen.

Oxycodone 45 mg po every 2 hours as needed for pain.

How Is the Patient Doing?

After a week, the patient reports that she is unhappy with the new regimen, despite better pain control. She complains that the regimen is too cumbersome because of the large number of pills, and she is reluctant to increase the dose further. She asks whether another pain medication can be tried.

ANOTHER SWITCH?

The decision is made to rotate the patient to an alternative long-acting opioid, specifically TFS. As

noted, clinical experience has suggested that conversion to this drug can usually be made without a reduction in the equianalgesic dose.

Here's How the Switch Was Done

1. The 24-hour dose of the previous opioid (including the fixed schedule dosage and the supplemental doses taken as needed) was calculated.

Extended-release oxycodone 240 mg po every 12 hours
= 480 mg/d

Oxycodone 45 mg po $\times$ 3 doses/d = 135 mg/d

Total: 480 mg + 135 mg = 615 mg of oxycodone per day

2. Although the conversion could be done using oral ratios based on the information in the package insert for TFS, the equianalgesic table also provides a method of calculation based on conversion from intravenous (IV) morphine. The oxycodone dose is converted to IV morphine using the equianalgesic table.

Oxycodone 20 mg po = morphine 10 mg IV

Oxycodone 615 mg/d po = morphine 308 mg/d IV

3. The 24-hour dose is converted to an hourly rate.

Morphine 308 mg IV/24 hours = 12.8 mg IV/h

4. The equianalgesic table indicates that one approach for the conversion to the TFS is based on the following ratio: morphine 4 mg IV/h = fentanyl 100 μ g/h.

Morphine 4 mg IV/h = TFS 100- μ g patch (delivers 100 μ g/h)

Morphine 13 mg IV/h = fentanyl 325 μ g/h. This is approximated as three TFS 100- μ g patches.

5. The patient took a last dose of extended-release oxycodone and applied three of the TFS patches to the skin at the same time. This overlap in dosing is important, given the delay required for a new therapy with the TFS to produce effects.

Selection of a Rescue Dose

A decision is made to add hydromorphone 22 mg po every 2 hours prn as a rescue dosage for the new regimen. Here's how the dosage was calculated:

1. The dose of TFS is converted to IV morphine using the equianalgesic table.

Fentanyl 100 μ g/h = morphine IV 4 mg/h

TFS 300 μ g/h = morphine IV 12 mg/h (or 288 mg/d IV)

2. The 24-hour dose of morphine is converted to oral hydromorphone.

Morphine 10 mg IV = hydromorphone 7.5 mg po

Morphine 288 mg IV = hydromorphone 216 mg po

3. The rescue dose is calculated as 5% to 15% of the total daily dose.

216 mg $\times$ 5% = 12.8 mg of hydromorphone po

216 mg $\times$ 10% = 21.6 mg of hydromorphone po

216 mg $\times$ 15% = 34.4 mg of hydromorphone po

How Is the Patient Doing?

The patient had a favorable reaction to the fentanyl, reporting fewer side effects and adequate analgesia. She remained stable for a month, then required an increase to four of the 100- μ g/h patches. When pain did not adequately subside, the dosing schedule was changed to every 48 hours. After a week, the patient called to report that pain was still poorly controlled and new side effects had appeared since the last dose increase. She was experiencing nightmares and jerking movements. She no longer liked the multiple patches and asked whether another medication could be tried.

ANOTHER SWITCH?

The patient is seen and examined. Various analgesic options are discussed, including reirradiation, a trial of intraspinal therapy, a nerve block, and trials of nonopioid drugs. She is impressed with the positive change that occurred when the opioid was switched before and requests one more trial of an alternative opioid. Methadone is suggested, and though the patient expresses concern initially ("Isn't that only for drug addicts?"), she responds well to education about the valuable analgesic properties of this drug and agrees to a trial. She is switched to methadone 20 mg po every 6 hours. Several approaches have been developed for the conversion to methadone.^{9,12,18,19} One approach initiates therapy with as-needed dosing; another starts with dosing on a fixed schedule (three to four times per day) in combination with an alternative rescue drug.

Here's How the Switch to Methadone Was Done

1. The 24-hour opioid dose (including fixed schedule dose and rescue doses) was calculated. During the previous few days, no rescue doses had been taken by the patient.

Four TFS 100- μ g patches = 400 μ g/h

2. The dose of fentanyl was converted to IV morphine.

Fentanyl 100 μ g/h = IV morphine 4 mg/h

Fentanyl 400 μ g/h = IV morphine 16 mg/h or 384 mg/d

3. The IV morphine dose was converted to an oral dose.

Morphine 10 mg IV = morphine 30 mg po

Morphine 384 mg IV = morphine 1,152 mg po

4. The oral morphine is converted to oral methadone using an equianalgesic table.

Morphine 30 mg po = methadone 20 mg po

Morphine 1,152 mg po = methadone 768 mg po

5. The dose of methadone is reduced by 90%, to 10% of baseline, and started as divided doses.

Methadone 768 mg $\times$ 10% = methadone 77 mg/d. The starting methadone dose is thus rounded to 20 mg po every 6 hours.

Choosing a Rescue Dose

Given the long half-life of methadone, the use of an alternative short half-life opioid is usually preferred for the rescue drug. In this case, the patient has agreed to use short-acting morphine 30 mg po every 2 hours as needed as the rescue dose. This dose was chosen based on the prior calculations. The patient has been using fentanyl at a dose approximately equivalent to 1,152 mg of oral morphine per day. If 50% of this quantity (the typical reduction in converting from fentanyl to morphine), or 576 mg, is used as the starting point for calculation of the rescue dose, then 30 mg represents approximately 5% of the total daily dose.

How Is the Patient Doing?

The patient discontinued the TFS and started the methadone. She needed several rescue doses per day during the initial 4 days but then stabilized. Analgesia was much improved, and aside from constipation, all the opioid-related side effects disappeared. Two months later, she continued to report adequate pain control.

For those patients who experience a poor response during routine opioid therapy, there are many strategies that can be implemented to improve analgesia. Opioid rotation is a simple strategy and within the purview of all clinicians. With a comprehensive assessment, a practical knowledge of the equianalgesic dose table, and a commitment to reassess and adjust therapy, clinicians can pursue this approach and potentially identify the most favorable opioid for an individual patient.

REFERENCES

1. Jacox A, Carr DB, Payne R, et al: Management of Cancer Pain: Clinical Practice Guideline—No. 9 (AHCPR publication no. 94-0592). Rockville, MD, Agency for Health Care Policy and Research, US Department of Health and Human Services, Public Health Service, 1994
2. Portenoy RK: Contemporary Diagnosis and Management of Pain in Oncological and AIDS Patients, ed 3. Newtown, PA, Handbooks in Health Care Company, 2000
3. Portenoy RK: Managing cancer pain poorly responsive to systemic opioid therapy. *Oncology* 13:25-29, 1999
4. Mercadante S, Portenoy RK: Opioid poorly responsive cancer pain: Part 3. Clinical strategies to improve opioid responsiveness. *J Pain Symptom Manage* 21:338-354, 2001
5. Mercadante S, Portenoy RK: Opioid poorly-responsive cancer pain: Part 1. Clinical considerations. *J Pain Symptom Manage* 21:144-150, 2001
6. Galer BS, Coyle N, Pasternak GW, et al: Individual variability in the response to different opioids: Report of five cases. *Pain* 49:87-91, 1992
7. Cherny NI, Chang V, Frager G, et al: Opioid pharmacotherapy in the management of cancer pain: A survey of strategies used by pain physicians for the selection of analgesic drugs and routes of administration. *Cancer* 76:1288-1293, 1995
8. Bruera EB, Pereira J, Watanabe S, et al: Systemic opioid therapy for chronic cancer pain: Practical guidelines for converting drugs and routes. *Cancer* 78:852-857, 1996
9. Derby S, Chin J, Portenoy RK: Systemic opioid therapy for chronic cancer pain: Practical guidelines for converting drugs and routes of administration. *CNS Drugs* 9:99-109, 1998
10. Lawlor P, Turner K, Hanson J, et al: Dose ratio between morphine and hydromorphone in patients with cancer pain: A retrospective study. *Pain* 72:79-85, 1997
11. Houde RW, Wallenstein SL, Beaver WT: Evaluation of analgesics in patients with cancer pain, in Lasagna L (ed): *International Encyclopedia of Pharmacology and Therapeutics*. Oxford, United Kingdom, Pergamon Press, 1966, pp 59-98
12. Anderson R, Saiters JH, Abram S, et al: Accuracy in equianalgesic dosing: Conversion dilemmas. *J Pain Symptom Manage* 21:397-406, 2001
13. Mancini I, Lossignol DA, Body JJ: Opioid switch to oral methadone in cancer pain. *Curr Opin Oncol* 12:308-313, 2000
14. Ripamonti C, Groff L, Brunelli C, et al: Switching from morphine to oral methadone in treating cancer pain: What is the equianalgesic ratio? *J Clin Oncol* 16:3216-3221, 1998
15. Bruera EB, Pereira J, Watanabe S, et al: Opioid rotation in patients with cancer pain. *Cancer* 78:852-857, 1996
16. Shimoyama N, Shimoyama M, Megumi S, et al: D-Methadone is antinociceptive in rat formalin test. *J Pharmacol Exp Ther* 283:648-652, 1997
17. Elliot K, Hynanski A, Inturrisi CE: Dextromethorphan attenuates and reverses analgesic tolerance to morphine. *Pain* 59:361-368, 1994
18. Hagen NA, Wasylenko E: Methadone: Outpatient titration and monitoring strategies in cancer patients. *J Pain Symptom Manage* 18:369-375, 1999
19. Mercadante S, Casussio A, Calderone L: Rapid switching from morphine to methadone in cancer patients with poor response to morphine. *J Clin Oncol* 17:3307-3312, 1999