Palliative Care Review

Opioid Therapy in the Seriously Ill: Optimizing Analgesic Outcomes

Expertise in the administration of opioid analgesics is the foundation of pain management in the seriously ill. The clinician should have knowledge of opioid pharmacology and a clear grasp of practical guidelines for dosing. The goal of long-term opioid treatment is to provide clinically meaningful pain relief with tolerable side effects and overall benefit to quality of life. This involves managing the risks associated with opioids, both side effects and the risk of substance abuse outcomes, and administering the drugs in a manner that optimizes analgesic outcomes. This presentation is about best practices for optimizing pain relief.

Selection of an Opioid

The opioids conventionally used orally for moderate pain in patients with limited prior opioid exposure include hydrocodone and oxycodone, combined with aspirin or acetaminophen. Tramadol and, more recently, tapentadol are centrally-acting analgesics with a mechanism that is partly opioid and partly related to monoamine (e.g., norepinephrine) reuptake inhibition that may be used. Evidence-based guidelines issued by the European Association for Palliative Care specifically exclude codeine because its genetically determined variability in metabolism to morphine introduces variability and risk. Meperidine also is not included because of the potential for adverse effects related to neurotoxic metabolites.

Pain that is generally severe is conventionally treated with a single-entity pure μ agonist opioid, such as morphine, fentanyl, oxycodone (without acetaminophen or aspirin), hydromorphone, oxymorphone, levorphanol, and methadone. Single-entity long-acting hydrocodone can now be added to this list (Table 1).

There is large individual variation in the response to different opioids, and there is not one preferred opioid. The decision to choose one over another is usually based on the available formulation, cost, prior experience, and some drug-related factors. Therapeutic failure with one drug may be followed by remarkable success with another.

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Table 1: Opioid Analgesics Used for the Treatment of Chronic Pain

Drug	Equianalgesic (mg) Doses	Half-life (hr)	Duration (hr)	Comments
Hydrocodone	30 PO	3-4	4-8	Used for moderate pain in a combination product containing a non-opioid.
Modified-release hydrcodone	30 PO	—	8-12	
Morphine	10 IM/IV/SQ 20-30 PO	2-3 2-3	3-4 3-6	Standard for comparison for opioids; multiple routes available.
Modified-release morphine	20-30 PO	2-3	8-12	
Sustained-release morphine	20-30 PO	2-3	12-24	
Hydromorphone	1.5 IM/IV/SQ 7.5 PO	2-3 2-3	3-4 3-6	Potency and high solubility may be beneficial for patients requiring high opioid doses and for subcutaneous administration.
Modified-release hydromorphone	7.5 PO	2-3	24	
Oxycodone	20-30 PO	2-3	3-6	Available as a single entity or combined with aspirin or acetaminophen.
Modified-release oxycodone	20-30 PO	N/A	8-12	
Oxymorphone	1 IM/IV./SQ 15 PO	— —	3-6 4-6	
Modified-release oxymorphone	15 PO	N/A	12	
Levorphanol	2 IM/IV/SQ 4 PO	12-15 12-15	3-6 3-6	With long half-life, accumulation possible after beginning or increasing dose.
Methadone	10 IM/IV/SQ 20 PO	12-150	6-8	May be far more potent than indicated in the table, presumably because potency of available racemate due in part to the d-isomer, a NMDA antagonist that may reverse tolerance and augment analgesia; with highly variable half-life, patients require greater vigilance for weeks, until steady state has definitely occurred; also can prolong the QTc interval and in most cases baseline ECG, and repeat ECG's during dose titration, should be checked.
Fentanyl	50 – 100 µg IV/SQ	7-12	1-2	Can be administered as a continuous IV or SQ infusion.
Fentanyl transdermal system		N/A	48-72 per patch	Refer to package insert for oral and parenteral medication equianalgesic dosing guidelines. Not usually recommended for opioid naïve patients in currently available doses. Not recommended for acute pain.
Transmucosal fentanyl citrate formulations		7-12	1-2	New formulations indicated for the treatment of breakthrough pain. Varied products, including intraoral, buccal tablet, buccal patch, sublingual, and intranasal formulations. Not recommended for opioid naïve patients. Initial dose always should be one of the lowest doses available, even if the patient is receiving a relatively high dose of a scheduled opioid.

In recent years, the role of methadone has expanded. Methadone's low cost, relatively high potency, and long half-life could be favorable characteristics. However, its use presents challenges. The elimination half-life is variable, ranging from about 12 hours to almost a week. Uncertain potency means that a switch to methadone from another drug requires a large (75-90%) reduction in the calculated equianalgesic dose; if the calculated dose is higher than 40 mg/day, dosing is usually initiated at this level nonetheless. Because QTc prolongation is possible, methadone should be used cautiously in patients at risk for arrhythmia or receiving other drugs that could prolong the QT interval; an ECG usually should be checked before it is started and at least once as titration occurs.

Routes of Administration

The oral and transdermal routes are used conventionally for chronic pain with alternative routes considered for specific reasons. If these routes are not available, the SQ route usually is preferred. Ambulatory infusion via a subcutaneous route has been made possible with the development of small infusion pumps.

Dosing Considerations

Individualization of dose is the key to optimizing treatment outcomes. Inadequate adjustment of the dose is probably the most common reason for unsuccessful long-term management of cancer pain. In all cases, the dose of an opioid should be increased until acceptable analgesia is produced or intolerable and unmanageable side effects supervene. Relatively opioid-naïve patients with moderate pain usually are treated with an available combination tablet, which includes a short-acting opioid and may be administered as needed or on a fixed schedule. Patients with severe pain and those who do not respond to a drug used conventionally for moderate pain may be treated with a single entity opioid recommended for severe pain. After the need for continual treatment is established with a short-acting drug, most patients are switched to long-acting drugs to improve convenience and adherence.

Most patients require dose titration, which may be done on a percent basis—increasing the dose by 30-50% every few days. If, however, the patient also is given a PRN 'rescue dose' for breakthrough pain, the increase in the dose of the long-acting drug may be done by adding up the supplemental, as-needed, doses and then increasing the long-acting dose by a comparable amount.

Drugs for Breakthrough Pain

Breakthrough pain is highly prevalent, and the use of as-needed "rescue doses" provides a means of treating these transitory pains. Clinical experience suggests that an immediate-release short-acting drug should be used for these supplemental doses. With the exception of methadone, this can generally be the same drug administered on an around-the-clock basis. The usual approach involves a short-acting oral drug prescribed every 2 hours as needed at a dose equal to 5% to 15% of the total daily opioid consumption. Alternatively, breakthrough pain can be treated with rapid-onset transmucosal fentanyl products including lozenge, buccal patch, sublingual tablet, and nasal spray formulations. These drugs have been shown to be safe and efficacious when used to treat breakthrough pain in cancer patients receiving a fixed-schedule opioid regimen for persistent pain, and their onset of action is faster than an oral drug. Cost is a consideration, however, and the ultimate role of rapid-onset formulations in the treatment of breakthrough pain remains to be defined.

Opioid Rotation

When patients do not have a satisfactory outcome, they may be considered to be poorly responsive to the specific drug and route. A common strategy at this juncture is opioid switching, or "rotation." Opioid rotation uses information in the equianalgesic dose table. A guideline (Table 2) starts with the calculated equianalgesic dose and incorporates dose reductions based on the assumption of incomplete cross-tolerance between drugs, combined with the need to apply clinical judgment. It also highlights the exception of methadone, the dose of which must be calculated with a larger correction factor in the expectation of a higher-than-expected potency.

Table 2: Guideline for Opioid Rotation

Step 1

Calculate the equianalgesic dose of the new opioid based on the equianalgesic table.

- If switching to any opioid other than methadone or fentanyl, identify an "automatic dose reduction" of 25% to 50% lower than the calculated equianalgesic dose.
- If switching to methadone, identify this window at 75% to 90% lower than the calculated equianalgesic dose.
- If switching to transdermal fentanyl, calculate dose conversions based on the equianalgesic dose ratios included in the package insert for these formulations.
- Select a dose closer to the upper bound (50% reduction) or the lower bound (25% reduction) of this automatic dose reduction window on the basis of a clinical judgment that the patient is more or less frail.

Step 2

Perform a second assessment of pain severity and other medical or psychosocial characteristics to determine whether to apply an additional increase or decrease of 15-30% to enhance the likelihood that the initial dose will be effective for pain, or conversely, unlikely to cause withdrawal or opioid-related side effects.

Assess initial response and titrate the dose of the new opioid regimen to optimize outcomes.

Adjust the 'rescue dose' as needed.

Portenoy RK. Treatment of cancer pain. *Lancet.* 2011;377:2236-2247

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