Techniques of opioid administration

Moutaz Burwaiss

Dee Comerford

Abstract

Opioids continue to be the main pharmacological treatment for severe acute pain. Traditional methods of opioid administration (oral, intramuscular, subcutaneous and intravenous) are more effective in managing pain if their treatment regimens are individualized and dosages are titrated to effect. Transdermal delivery of highly lipid-soluble opioids is an alternative route of treatment when managing severe pain in chronic conditions and palliative care scenarios.

Keywords Acute pain; analgesia; patient-controlled analgesia; postoperative pain; transdermal

Royal College of Anaesthetists CPD matrix: 1D02

Introduction

Opioids continue to be the main pharmacological treatment for severe acute pain. The management of acute pain has improved with the introduction of advanced techniques for the administration of opioids (e.g. patient-controlled analgesia (PCA) and epidural analgesia) and the more recent innovative non-invasive modalities. However, the traditional methods of administration still remain in common use.

Conventional routes

The key to making opioid administration more effective is to individualize treatment regimens for patients by titrating the drug dose and frequency to suit the patient. The principle is to titrate the dose against the effect and minimize adverse effects. If the drug has been delivered and absorbed and the patient still complains of pain then it is safe to administer another smaller dose (5 minutes after an intravenous (IV) injection, 60 minutes after an intramuscular (IM) or subcutaneous (SC) injection and 90 minutes after oral morphine). If the second dose is ineffective, repeat the process or change the route of administration to achieve faster pain control.

Moutaz Burwaiss *MBChB FRCA is a Consultant Anaesthetist and Pain Specialist at Glasgow Royal Infirmary, Glasgow, UK. Conflicts of interest: none declared.*

Dee Comerford *MSc is Lead Specialist Nurse in Pain Services at Singleton Hospital, Abertawe Bro-Morgannwg University Local Health Board (ABMULHB – Formerly Swansea NHS Trust), UK. Conflicts of interest: none declared.*

Oral opioids

Oral opioids are available as immediate-release (IR), such as oramorph, sevredol and oxynorm and slow-release (SR) preparations such as MST and Oxycontin. SR preparations are also called extended release, prolonged release or controlled release. IR opioids have a fast onset of action, in most cases analgesia is obtained in 45–60 minutes and their duration of action is usually around 3–4 hours. SR preparations generally take 3–4 hours to reach their peak effect and will have a longer duration of action (12–24 hours). SR preparations should not be used as the sole agent for the treatment of acute pain as their onset times make them difficult to titrate. However their use at fixed intervals in conjunction with IR preparations for breakthrough pain is effective. To do so, calculate the equivalent total daily dose of oral opioid and divide by two to determine the 12 hourly doses, rounding down to the closest tablet strength.[1]

In the acute setting, oral opioids can be used as step-down analgesia from epidurals or PCAs. Morphine is the gold standard to which all other opioids are compared. Oral morphine has a bioavailability of around 30%; therefore 10 mg of IV morphine is roughly equivalent to 30 mg of oral morphine. These ratios are only a guide. Inter-patient variability requires that each patient be carefully titrated to an appropriate dose. Other SR opioids can also be used for step-down analgesia. Table 1 lists commonly quoted equianalgesic conversion ratios. Once the estimated oral morphine dose has been calculated, this can then be converted to a second opioid. These conversion ratios are more frequently utilized in the management of chronic non-malignant pain (CNMP) and malignant pain where opioid rotation may be considered. Conversion ratios should be used with caution as they are largely based on single-dose studies in opioid-naïve patients and do not take into account incomplete cross-tolerance.[2] The calculated equianalgesic dose should be reduced by 25–30% and the patient should be monitored for signs of toxicity or withdrawal on commencement of new opioid.

Oxycodone differs from oral morphine in that it has a higher bioavailability (up to 87%) and a slightly longer half-life. When using IR oxycodone, pain relief occurs as early as 15 minutes and peaks at approximately 1 hour.[1] The usual adult dose is 10–30 mg every 4 hours as needed for pain relief, although four times a day dosing regimens have also proved to be effective. The use of SR oxycodone is indicated for the treatment of moderate-to-severe pain when continuous analgesia is required for prolonged periods. The release of oxycodone from Oxycontin is biphasic. Therefore, initially there is a relatively rapid release followed by a more controlled release allowing for quicker onset of analgesia and a long duration of action.

A new oral preparation (Targinact™) combines oxycodone with naloxone. As both drugs enter the gut the naloxone preferentially binds to the opioid receptors present and markedly reduces opioid induced constipation. Due to first pass metabolism 97% of the naloxone is eliminated and allows Oxycontin to enter the systemic circulation to exert it's analgesic effect unchallenged.

Tapentadol is a strong mu opioid agonist, which also inhibits noradrenaline reuptake. It is available in IR and SR preparations. The IR preparation is indicated for moderate to severe acute pain in adults while the prolonged release preparation is for the management of severe chronic pain in adults. It is clinically effective in the management of nociceptive and neuropathic chronic pain conditions.

Equianalgesic doses and half-lives of common opioids

Opioid	IM/IV (mg)	Oral (mg)	Oral conversion ratio (morphine:opioid)	Half-life (hours)
Morphine	10	30	1:1	2–3
Oxycodone	14	20–30	1.5:1	2–3
Hydromorphone	1.5	7.5	5:1	3–4
Methadone	10	10–15	Dependent on morphine dose	15–40
Tapentadol	10	30	1:2.5	4
Codeine	130	200	1:6	2–4
Tramadol	100	100	1:5	5–7
Pethidine	100	400	–	3–4
Buprenorphine patch	–	–	75:1	10–36
Fentanyl patch	–	–	As per product information	22–25

Published reports vary in the suggested doses considered to be equianalgesic with morphine. Therefore, titration to clinical response in each patient is necessary. Suggested doses are the result of single-dose studies in opioid-naïve patients, therefore, use of data to calculate total daily dose requirements may not be appropriate. There may be incomplete cross-tolerance between drugs. In patients who have been receiving one opioid for a prolonged period, it is recommended to reduce the calculated equianalgesic dose by 25–30% and then titrate to response. IM, intramuscular; IV, intravenous.

Sources: 1. Prescription opioid policy. RACP, FPMANZCA, RACGP, RANZCPsych. April 2009. 2. Macintyre PE, Ready LB. Acute pain management: a practical guide, 2nd edn. London: WB Saunders, 2001. 3. Mercadante S, Caraceni A. Conversion ratios for opioid switching in the treatment of cancer pain: A systematic review. *Palliat Med* 2011; **25**(5): 504–515.

Table 1

Rectal opioids

Rectal opioid suppositories may be useful in patients unable to take oral medication and in whom other methods are unsuitable. Drug absorption varies with the site of placement in the rectum, the contents of the rectum and its blood supply. Drugs absorbed from the lower half of the rectum drain into the inferior and middle rectal veins and then into the inferior vena cava therefore avoiding first pass metabolism. Contraindications to this route would be previous colorectal surgery and a rectal lesion. Suppository formulations containing morphine, oxycodone or hydromorphone are available.

Intramuscular and subcutaneous injections

Intramuscular and subcutaneous injections of opioids are commonly used for the treatment of moderate to severe acute pain and are a useful route if there is a lack of personnel trained to administer intravenous injections or if continued venous access is difficult. Absorption depends on the perfusion of the chosen site for injection. During periods of low perfusion (hypovolaemia, shock, hypothermia) absorption will be minimal resulting in poor analgesia. However, when perfusion improves the patient may be subject to a large dose of opioid entering into the systemic circulation.

The use of algorithms and guidelines for intramuscular administration has become increasingly popular in the management of acute pain (Figure 1). As the rate of absorption of morphine after subcutaneous injection is similar to that of intramuscular injection the guidelines for titration are the same.

Subcutaneous injection via an indwelling cannula in the subcutaneous tissue of the upper outer aspect of the arm or thigh is a useful alternative to intramuscular administration. The subcutaneous route is less invasive, has a higher patient acceptability rate and reduced risk of nerve injury. It is a useful method of administration in cancer patients who cannot tolerate opioid medications by other routes.

Advanced methods of administration

Intravenous bolus

Intravenous bolus is a superlative means of establishing rapid analgesia. It may be used: for patients who are hypotensive or hypovolaemic, when absorption of the drug after intramuscular or subcutaneous administration is less predictable; to achieve initial pain relief (e.g. after surgery or trauma); and, to deal with episodes of inadequate analgesia or incident pain. The technique is often limited to specialized areas where nursing staffs are trained in the use of an algorithm for the administration of intravenous opioids (Figure 2). There is less variability in blood levels if smaller doses are administered more often, making it easier to titrate the drug to suit each patient. The maximum effect of intravenous fentanyl may be seen within 5 minutes, whilst intravenous morphine may take up to 15 minutes. The time to peak effect must be considered when dosing intervals are prescribed.

Intravenous infusions

Intravenous infusions of opioids are used to obtain stable analgesic levels thereby avoiding the peaks and troughs of intermittent bolus doses. Steady state plasma levels however require four to five half-lives of the infused opioid to reach (Table 1). This slow onset time together with inter-patient variability in response to opioids make this technique difficult to use and may result in the inadequate treatment of pain or delay the onset of side effects such as respiratory depression. Consequently this route is limited to specialized areas. If used, IV bolus doses should be used to obtain analgesia before commencing the infusion. Similarly, if breakthrough pain occurs, bolus doses are required to re-establish analgesia before the background rate is increased.

Intravenous patient-controlled analgesia

Intravenous patient-controlled analgesia (IV PCA) allows the patient to self administer a predetermined dose of opioid within the constraints of a lockout period, resulting in less variability in the blood levels of the drug, thereby enabling titration of the drug to effect.