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; post-operative pain; transdermal

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.

Oral opioids
Oral opioids are available as immediate-release (IR), such as oral morph, sevedol 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.

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. 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. 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 μ 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.

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Equianalgesic doses and half-lives of common opioids

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

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.


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.
The analgesic efficacy of epidural opioids is greater than parenteral opioid administration, resulting in superior pain relief despite a smaller epidural dose (e.g. epidural morphine, 2–3 mg: intramuscular morphine, 10 mg). This depends on the lipid solubility of the opioid used (Table 3). With highly lipid-soluble drugs (e.g. fentanyl) there is little difference in the dose required by either route to produce a similar analgesic effect.

The doses of drugs required for intrathecal analgesia are much smaller than those for epidural analgesia (e.g. for morphine, an epidural dose of 2–3 mg would equate to 0.2–0.3 mg as an intrathecal dose). Opioid solutions formulated for spinal administration are available and should be used because other formulations may contain potentially neurotoxic preservatives.

Long-acting intrathecal opioids, administered as a one-off spinal injection with or without local anaesthetics, can be used for prolonged analgesic effects in a variety of settings (orthopaedics, genitourinary, obstetrics). They are increasingly being utilized for colorectal and gynaecological surgery within an enhanced recovery programme pathway.

Transmucosal and transdermal administration

Fentanyl and buprenorphine are the most commonly used opioids for these methods of administration due to their high potency (100 and 75 times more potent than morphine respectively), lipophilicity and low molecular weight. Administration via these routes avoids hepatic first pass metabolism.

Buccal and sublingual

Fentanyl is available as a lozenge with an applicator (often referred to as a fentanyl lollipop) and as a buccal tablet. Both are licensed for breakthrough pain in opioid-tolerant cancer patients.

As the lozenge is applied to the buccal mucosa it dissolves and 25% of the total fentanyl dose is absorbed rapidly. Analgesia occurs in around 5 minutes with peak plasma concentrations occurring at 22 minutes. The remaining 75% is swallowed and is subjected to high first pass metabolism. This latter method of administration is slower and maintains analgesic concentrations for around 2 hours. Total overall bioavailability is around 50%.

The fentanyl buccal tablet (FBT) effervesces in the buccal mucosa resulting in greater fentanyl absorption transmucosally (50%). The remainder is absorbed via the gastrointestinal tract. Absolute bioavailability is 65%. Therefore a greater proportion of the total fentanyl dose is available with a shorter onset time. With this in mind, FBT doses should be decreased by 30% compared to the lozenge dose to achieve comparable systemic fentanyl concentrations.

Buprenorphine is absorbed through the sublingual mucosa within minutes. Peak concentrations are achieved within 2–4 hours and terminal half-life is around 5 hours. Absolute bioavailability is around 35%. Sublingual buprenorphine is indicated for the short-term relief of moderate-to-severe pain including postoperative and terminal pain.

Intranasal

Intranasal opioids are a useful alternative to the intravenous or intramuscular routes for the treatment of acute pain in children. The nasal mucosa is well perfused allowing for rapid absorption. Due to the small surface area of the nasal mucosa, opioids must be given in small volumes and at high concentrations to avoid run-off into the pharynx. Use of both nostrils doubles the absorptive capacity and use of atomized particles also enhances absorption. Fentanyl bioavailability is estimated to be around 70% by this route and time to maximum plasma concentrations is 5 minutes. Buprenorphine bioavailability is estimated to be 48%. Diamorphine can also be administered in this fashion and can be reconstituted into a small volume.

### Table 3

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Parenteral Dose</th>
<th>Epidural Dose</th>
<th>Intrathecal Dose</th>
<th>Spinal Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>40–65 kg: 7.5 mg</td>
<td>10 mg</td>
<td>2 mg</td>
<td>0.2 mg</td>
</tr>
<tr>
<td>Pethidine</td>
<td>40–65 kg: 50 mg</td>
<td>75 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1**

Rather like a continuous infusion, IV bolus doses will be required to establish analgesia prior to the PCA commencing. Table 2 lists commonly prescribed IV PCA variables for opioid-naïve patients.
volume. Adverse effects relating to the intranasal route are burning, stinging in the nose and nasal pruritus.7

**Pulmonary**
The lungs offer a highly vascularized surface area (>90 m²) for opioid absorption. Nebulized opioids have been investigated for several indications, including pain relief after surgery, the provision of analgesia in general practice and the symptomatic control of dyspnoea in palliative care. Absorption by this route is unpredictable and variable; therefore, it is unlikely to be used for acute pain relief.

**Intra-articular**
Several reviews indicate that morphine, 5 mg, injected into the knee joint at the end of surgery may provide postoperative pain relief for up to 24 hours, and may have some effect in reducing the need for analgesia.4

**Transdermal**
Transdermal drug delivery relies on passive diffusion into the skin. Onset time is slow and plasma levels are stable. This provides an increased duration of therapeutic effect and reduces the need for frequent dosing. Fentanyl and buprenorphine are available for transdermal delivery (Durogesic, Butrans, Transtec) for management of moderate-to-severe malignant and CNMP.

Matrix patches have largely superseded reservoir systems. The drug is contained within the adhesive film of the patch rather than a separate reservoir layer. This allows the patch to be smaller, thinner and more flexible while delivering equal rates of opioid. Drug leakage and the potential for abuse are also lowered. A significant amount of opioid remains in the patch after removal demanding patches be discarded appropriately. Body temperatures of greater than 40°C can increase absorption rates by one-third.5

Fentanyl patches can deliver 12.5, 25, 50, 75 and 100 µg/hour. There is a lag time of around 24 hours before therapeutic serum concentrations are achieved and 48 hours are required before assessing the adequacy of the dose. At least 4 days are required before steady state plasma levels are reached. These factors make transdermal routes unsuitable for the management of acute pain.

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**Figure 2**

Protocol for the administration of intravenous opioids in the recovery room in adults over 16 years

Pain score is 2 or 3 at rest or on movement

- Pain protocol and opioids prescribed?
  - Yes
  - If yes, prepare in sodium chloride 0.9%:
    - Diamorphine 5 mg in 10 ml
    - Morphine 10 mg in 10 ml
    - Fentanyl 100 µg in 10 ml
    - Pethidine 100 mg in 10 ml
  - No

- Respiratory rate > 8/minute
  - Yes
  - Sedation score < 2
  - Systolic blood pressure > 95 mmHg
  - Saturation > 90%
  - Temperature > 35°C
  - No

- If pain score is 3 (at rest or on movement) give:
  - 4 ml IV (< 65 years and > 40 kg)
  - 2 ml IV (> 65 years or < 40 kg)

- If pain score is 2 (at rest or on movement) give:
  - 2 ml IV (< 65 years and > 40 kg)
  - 1 ml IV (> 65 years or < 40 kg)

- Record dose

- Wait 3 minutes

- Routine observations and pain/sedation scores

- Seek advice from anaesthetist
  - Consider naloxone

- Pain scores:
  - 0 = no pain
  - 1 = mild pain
  - 2 = moderate pain
  - 3 = severe pain

- Sedation scores:
  - 0 = awake and alert
  - 1 = drowsy, responds to name only
  - 2 = very drowsy, responds to shaking
  - 3 = unrousable, unresponsive to shaking

Source: Pain Management Service, Swansea NHS Trust

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IV, intravenous.
On removal of the patch, 30% of the total delivered dose remains in the skin giving a terminal elimination half-life of 22–25 hours. Buprenorphine is delivered transdermally by way of a matrix system (Butrans 5–20 mg/hour, Transtec 35–70 mg/hour). As with fentanyl, buprenorphine has a long onset time. Minimum effective therapeutic concentrations are achieved in 24 hours. Peak concentrations are achieved after 60 hours; therefore the dose should not be increased before 3 days. After removal of the patch, buprenorphine concentrations decrease by 50% in 10–36 hours.

REFERENCES

### Table 2

Commonly prescribed initial values for PCA variables in opioid-naive patients

<table>
<thead>
<tr>
<th>Loading dose: usually 0 mg</th>
<th>Best to titrate for each patient before starting PCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incremental dose (bolus dose):</td>
<td>Consider starting with doses half these amounts in patients &gt;70 years</td>
</tr>
<tr>
<td>Morphine, 1 mg</td>
<td>The dose may need to be increased if analgesia is inadequate</td>
</tr>
<tr>
<td>Pethidine, 10 mg</td>
<td>Best if standardized for each drug</td>
</tr>
<tr>
<td>Diamorphine, 0.5 mg</td>
<td></td>
</tr>
<tr>
<td>Fentanyl, 20 mg</td>
<td></td>
</tr>
<tr>
<td>Remifentanil,8 40 mg</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone, 0.2 mg</td>
<td></td>
</tr>
<tr>
<td>Tramadol, 10 mg</td>
<td></td>
</tr>
<tr>
<td>Oxycodone 1 mg</td>
<td></td>
</tr>
</tbody>
</table>

**Concentration:** variable

**Dose duration:** cannot be adjusted in most PCA machines but where this can be done, ‘stat’ (over 6 seconds) is the shortest dose duration

**Lockout period:** 5–8 minutes

**Background infusion:** usually 0 mg/hour

If used, the rate of infusion in mg/hour is usually no greater than the bolus dose in mg

Consider varying according to patient age

**1-hour or 4-hour limits**

| Morphine, 30 mg (or equivalent) in 4 hours | Consider omitting |

IV, intravenous; PCA, patient-controlled analgesia.

8 Only used for IV PCA in obstetric units (40 µg bolus with a 2-min lockout).


### Table 3

Examples of epidural opioids

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Bolus (mg)</th>
<th>Onset (minutes)</th>
<th>Peak effect (minutes)</th>
<th>Duration (hour)</th>
<th>Infusion (mg/hour)</th>
<th>Lipid solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>1–6</td>
<td>20–30</td>
<td>30–60</td>
<td>6–24</td>
<td>0.10–0.75</td>
<td>1</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1–2</td>
<td>10–15</td>
<td>15–30</td>
<td>6–16</td>
<td>0.1–0.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Diamorphine</td>
<td>2–6</td>
<td>5–10</td>
<td>10–15</td>
<td>6–12</td>
<td>0.2–1.0</td>
<td>280</td>
</tr>
<tr>
<td>Pethidine</td>
<td>20–50</td>
<td>5–10</td>
<td>15–30</td>
<td>1–6</td>
<td>10–30</td>
<td>39</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.025–0.100</td>
<td>5–10</td>
<td>10–20</td>
<td>1–4</td>
<td>0.025–0.100</td>
<td>813</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>0.01–0.05</td>
<td>5–10</td>
<td>10–20</td>
<td>1–6</td>
<td>0.01–0.05</td>
<td>1780</td>
</tr>
</tbody>
</table>

a Effective dose varies depending on patient's age, medical condition and site of injection.

b Duration of analgesia varies widely; higher doses have longer duration of action.

c Octanol/pH 7.4 buffer partition coefficient. Values may vary according to different references.