Techniques of opioid administration

Dee Comerford

Abstract

Opioids continue to be the main pharmacological treatment for severe acute pain. Traditional methods of opioid administration (oral, intramuscular, subcutaneous) are more effective in managing pain if the treatment regimens are individualized and dosages are titrated to effect (pain relief). Oxycodone, an opioid agonist similar in potency to morphine, has proved useful as an oral step-down analgesic in the treatment of acute postoperative pain for a number of surgical procedures (orthopaedic, abdominal, gynaecological). It is also a valuable alternative opioid to morphine intravenous patient-controlled analgesia (IV PCA) in those patients who experience severe unpleasant side effects, such as nausea and hallucinations. Other PCA modalities available for opioid administration in the treatment of acute pain include epidural and transmucosal (intranasal, sublingual, buccal). Transdermal delivery of highly lipid-soluble opioids is available for the treatment of severe pain in chronic and palliative care. This passive drug delivery system is not suitable for the routine management of severe acute pain because rapid and reliable changes to the delivery rate are not possible. However, advances in transdermal delivery system technology have led to the development of a non-invasive PCA system for the management of acute postoperative pain, which utilizes the process of iontophoresis. This has the potential to be a valuable modality in the future management of acute postoperative pain.

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

Learning objectives

After reading this article, you should be able to:

- discuss the principle of opioid titration to effect
- explain the significance of lipid solubility in relation to analgesic efficacy and adverse effects
- identify the difference between transdermal and iontophoretic drug delivery.

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 and epidural analgesia) and the more recent innovative non-invasive modalities. However, the traditional methods of administration still remain in common use.

Conventional routes of administration

The key to making the traditional methods of 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 effect (pain relief) 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 injection, 60 minutes after an intramuscular or subcutaneous injection and 90 minutes after oral morphine). If this second dose is ineffective, repeat the process or change the route of administration to achieve faster pain control.

Oral opioids

Oral opioids are required in larger doses compared with the parenteral route to take into account the effect of first-pass metabolism in the liver. An equianalgesic dose of the parenteral opioid is required in the oral formulation (Table 1). Immediate-release oral

Equianalgesic doses and half-lives of common opioids

Opioid	i.m./i.v. (mg)	Oral (mg)	Half-life (hours)
Morphine	10	30	2–3
Pethidine	100	400	3–4
Oxycodone	14	20–30	2–3
Codeine	130	200	2–4
Fentanyl	0.15–0.20	–	3–5
Alfentanil	0.75–1.50	–	1–2
Sufentanil	0.02	–	2–3
Remifentanil	0.05–0.1	–	1–2
Diamorphine	5	60	0.5[a]
Methadone	10	10–15	15–40
Hydromorphone	1.5	7.5	3–4
Tramadol[b]	100	100	5–7
Buprenorphine	0.40	0.80[c]	3–5
Pentazocine	60	150	3–5
Nalbuphine	10–20	–	2–4
Butorphanol	2.0	–	2–3

- 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 results of single-dose studies only, 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 usually necessary to use a dose lower than the expected equianalgesic dose when changing to another opioid and titrating to effect.

Source: Macintyre PE, Ready LB. Acute pain management: a practical guide, 2nd edn. London: WB Saunders, 2001.

[a] Rapidly hydrolysed to morphine.
[b] Only part (about one-third) of its analgesic effect results from action on μ-opioid receptors.
[c] Sulingual. IM, intramuscularly; IV, intravenously.

Table 1

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. She qualified as an RGN at Morriston Hospital, Swansea, and worked in intensive care for 14 years before becoming Clinical Nurse Specialist in Pain Management in Carmarthenshire NHS Trust. She has an MSc in Pain Management from University Wales College of Medicine, Cardiff.*
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opioids (e.g. morphine (Oramorph, Sevredol), oxycodone, hydromorphone) are preferred for the management of acute pain, because, in most cases, analgesia is obtained in 45–60 minutes. Fixed-interval dosing (e.g. 4-hourly) is preferable to a 'when required' regimen to ensure adequate relief of moderate-to-severe pain. In addition, medication for breakthrough pain should be prescribed within a dose range based on the previous 24 hours' requirements.

Oxycodone as step-down analgesia: oral oxycodone has been used for, and proved to be effective in, the treatment of acute postoperative pain for many surgical procedures – abdominal, pelvic, breast, gynaecological, orthopaedic – on both an inpatient and a day-surgery basis.

Oxycodone differs from oral morphine in that it has a higher bioavailability (up to 87%) and a slightly longer half-life. An approximate conversion ratio of 1:1 is recommended between parenteral morphine and parenteral oxycodone. When transferring patients from parenteral to oral oxycodone, the dose should be based on a 1:2 ratio (i.e. 1 mg intravenous oxycodone:2 mg oral oxycodone). This same conversion ratio also applies when switching from parenteral morphine to oral oxycodone[1] (i.e. 1 mg intravenous morphine:2 mg oral oxycodone). These ratios are only a guide. Inter-patient variability requires that each patient is carefully titrated to an appropriate dose.

Dosage regimens: oxycodone's slightly longer half-life than morphine permits a 4- to 6-hourly dosing of the immediate-release oral formulation (Oxynorm) to maintain analgesia. Pain relief occurs as early as 15 minutes and peaks at approximately 1 hour.[1,2] The usual adult dose is 10–30 mg every 4 hour as needed for pain relief, although four times a day dosing regimens have also proved to be effective.

The use of controlled-release oxycodone (Oxycontin) is indicated for the treatment of moderate-to-severe pain when continuous analgesia is required for prolonged periods. Calculate the equivalent total daily dose of oral oxycodone and divide by 2 to determine the 12 hourly doses, rounding down to the closest tablet strength.[2]

A new oral preparation (Targinact™) combines this opioid agonist with an antagonist. As both oxycodone and naloxone enter the gut, naloxone has a much higher affinity for, and preferentially binds to, the opioid receptors counteracting opioid-induced constipation by blocking the binding of oxycodone. At least 97% of the naloxone is eliminated in the healthy liver, preventing it from significantly affecting analgesic efficacy; oxycodone passes through the liver into the central nervous system (CNS) where it exerts its analgesic effect.[3]

The maximum daily dose of Targinact is limited to 40 mg/20 mg (a dose ratio of 2:1 oxycodone hydrochloride to naloxone hydrochloride) corresponding to twice daily administration of Targinact 20 mg/10 mg prolonged-release tablets.[3]

Rectal opioid

Rectal opioid suppositories may be useful in patients unable to take oral medication and in whom other methods are unsuitable. Drugs absorbed from the lower half of the rectum bypass the portal vein and first-pass metabolism in the liver. Drug absorption varies with the site of placement in the rectum (the upper part of the rectum enters the portal system), the contents of the rectum and its blood supply. Suppository formulations containing morphine, oxycodone or hydromorphone are available.

Intramuscular injections

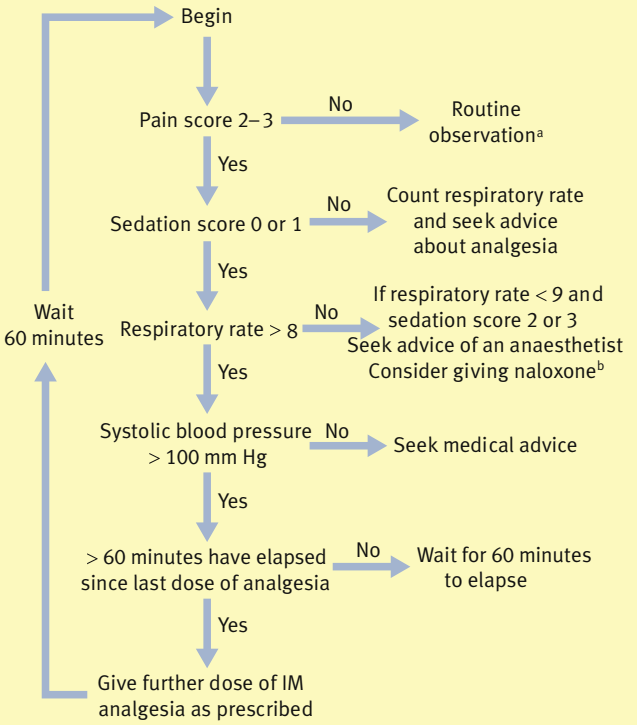
Intramuscular injections of opioids are useful in acute pain management if there is a lack of personnel trained to administer intravenous injections or if continued venous access is difficult. Traditionally, intramuscular opioids are prescribed 4-hourly as needed, but this fixed-interval dosing does not take into account the 2–4 hour half-life of typical opioids (Table 1). An intramuscular opioid injection takes 30–60 minutes to be effective. For a parenteral (or an enteral) opioid to be effective it must reach a certain therapeutic blood level, and this level may vary fourfold amongst patients. The most reliable indicator of opioid dose is the patient's age.[4] The use of algorithms and guidelines for intramuscular administration has become increasingly popular in the management of acute pain (Figure 1).

Protocol for hourly intramuscular injection of opioid analgesia in postoperative adult patients

Morphine hourly IM dose	
Weight	**Dose**
40–65 kg	7.5 mg
66–100 kg	10 mg

Pethidine hourly IM dose	
Weight	**Dose**
40–65 kg	50 mg
66–100 kg	75 mg

If weight is < 40 kg or > 100 kg seek advice of anaesthetist or APS



IM, intramuscular
[a] If the pain score is 1 and 4–6 hours have elapsed since the last intramuscular opioid injection, consider oral analgesia
[b] Respiratory depression: prepare and administer naloxone as per prescription until respiratory rate > 12 and sedation score < 2
See Figure 2 for pain and sedation scores
Source: Pain Management Service, Swansea NHS Trust

Figure 1

Subcutaneous injection

Subcutaneous injection via an indwelling cannula in the subcutaneous tissue of the upper outer aspect of the arm or thigh is a useful alternative route of administration. Morphine is most commonly used because pethidine is too irritating and painful when administered by this route as a single injection. As the rate of absorption of morphine after subcutaneous injection is similar to that of an intramuscular injection the guidelines for titration are the same (Figure 1).

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 may be used in the management of acute pain, thereby avoiding the varying levels of blood concentrations associated with bolus administration. It is difficult to predict the dose for an individual patient while preventing serious side effects (including respiratory depression). Consequently, this route is again limited to specialized areas.

An opioid infusion at a fixed rate takes five half-lives of the drug to reach a final steady-state concentration (Table 1).

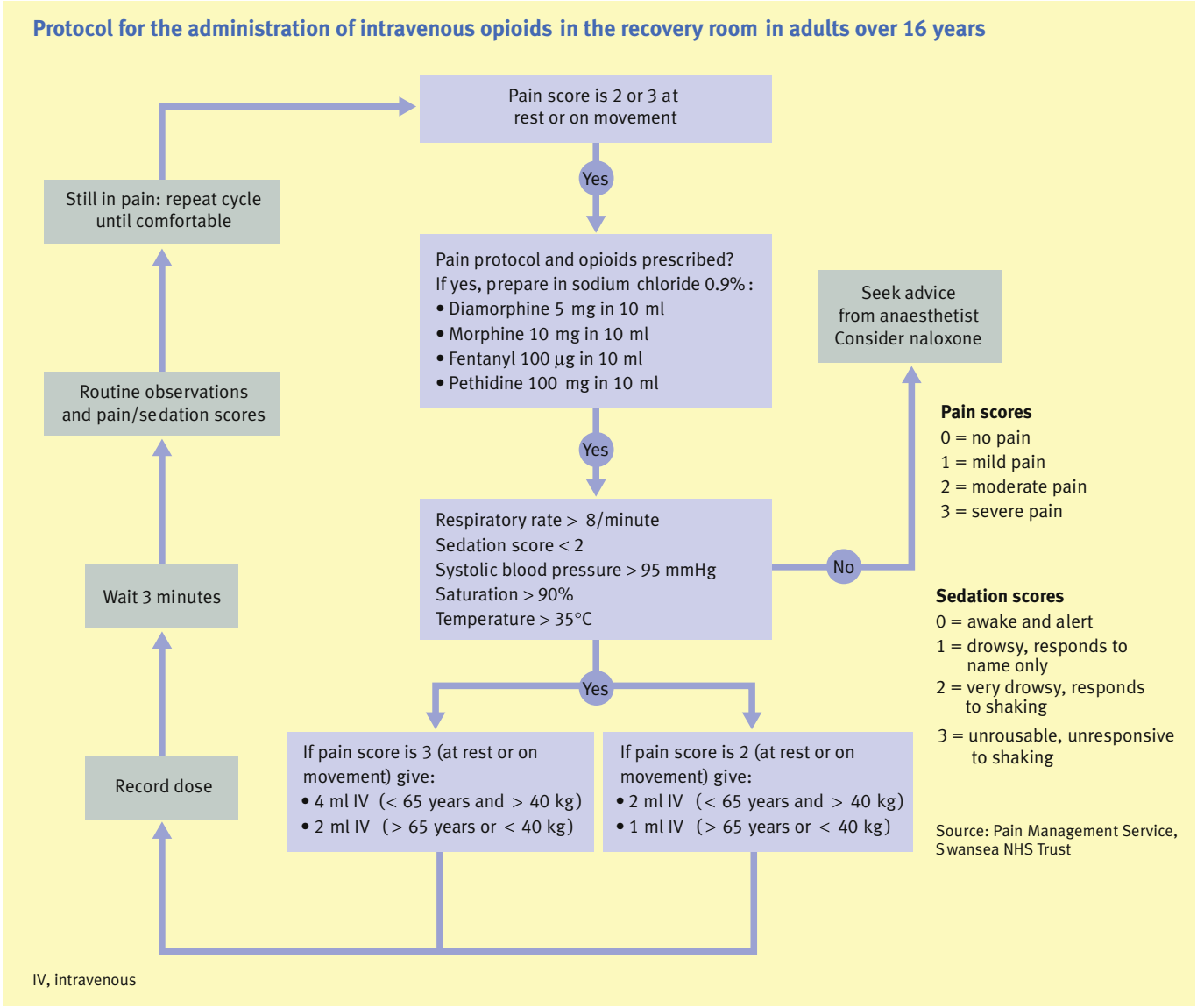


Figure 2

Therefore, pain relief will be obtained more rapidly with intravenous bolus dose administration before starting the opioid infusion. If breakthrough pain occurs, due to the inadequacy of the set continuous rate, intravenous bolus doses are required to re-establish pain relief before the infusion rate is increased because any alteration in the rate will take time to have an effect.

Intravenous patient-controlled analgesia

Intravenous patient-controlled analgesia (IV PCA) allows the patient to 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. (See pp 1–4 of this issue for a more detailed account of IV PCA). Table 2 lists commonly prescribed IV PCA variables for opioid-naïve patients.

Remifentanil PCA can be used in labour analgesia, as an alternative to an epidural when this is clinically contraindicated (e.g. coagulopathies) or declined by the patient. (See *Anaesthesia and intensive care medicine* **11**;7 2010 for a more detailed account of remifentanil IV PCA in obstetrics).

Epidural and intrathecal: these routes of delivery provide the most rapid analgesia of all available modalities, because of their direct application within the CNS. The advent of patient-controlled epidural analgesia (PCEA) allows patients to self-titrate the amount of drug they require on the basis of on individual analgesic need and may reduce the number of dosing adjustments required.[5]

Table 3 lists examples of commonly used epidural opioids. In general, the analgesic efficacy of epidural opioids is greater than parenteral opioid administration, resulting in superior pain relief despite the smaller epidural dose (e.g. epidural morphine, 2–3 mg:intramuscular morphine, 10 mg). This depends on the lipid solubility of the opioid drug 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).[4] 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 in combination with local anaesthetics, can be used for their 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.

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

Loading dose: usually 0 mg	Best to titrate for each patient before starting PCA
Incremental dose (bolus dose):	
Morphine, 1 mg	Consider starting with
Pethidine, 10 mg	doses half these amounts
Diamorphine, 0.5 mg	in patients >70 years
Fentanyl, 20 μg	The dose may need to be
Remifentanil,[a] 40 μg	increased if analgesia is
Hydromorphone, 0.2 mg	inadequate
Tramadol, 10 mg	Best if standardized for
Oxycodone 1 mg	each drug
Concentration: variable	
Dose duration: cannot be adjusted in most PCA machines but where this can be done, 'stat' (over 6 s) 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.
Source: Macintyre PE, Ready LB. Acute pain management: a practical guide, 2nd edn. London: WB Saunders, 2001.
[a] Only used for IV PCA in obstetric units (40 μg bolus with a 2-minute lockout).

Table 2

Transmucosal opioid administration

Intranasal: high-concentration, small-volume lipid-soluble opioids (e.g. fentanyl, diamorphine), are more suited to this route. They result in rapid absorption as a consequence of the perfusion properties of the nasal mucosa and have no hepatic first-pass effect. Intranasal PCA fentanyl, 25 μg/5 minutes, pethidine, 27 mg/5 minutes, and diamorphine, 0.5 mg/5 minutes, have been studied in the postoperative adult population and are as equally effective as IV PCA in treating postoperative pain.[6,7]

Mucosal: mucosal absorption of drugs from the oral cavity (sublingual and buccal) is rapid and circumvents first-pass metabolism. Opioid preparations, such as the fentanyl citrate lozenge, 200 μg over 15 minutes, or buprenorphine, 200–400 μg/8 hours, are used in the management of moderate-to-severe pain in acute, chronic and palliative care. The lozenge (often referred to as a fentanyl lollipop) has been used for 'breakthrough' pain relief in opioid-tolerant patients and for 'incident-pain' analgesia. Buprenorphine must be administered sublingually because if absorbed from the gastrointestinal tract almost the entire drug is metabolized, rendering it ineffective.

Pulmonary: nebulized inhalation administration of opioids, such as morphine, diamorphine, fentanyl and hydromorphone, has been investigated for several indications,[5] 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]

Examples of epidural opioids

Opioid	Bolus[a] (mg)	Onset (minutes)	Peak effect (minutes)	Duration[b] (hours)	Infusion[a] (mg/hour)	Lipid solubility[c]
Morphine	1–6	20–30	30–60	6–24	0.10–0.75	1
Hydromorphone	1–2	10–15	15–30	6–16	0.1–0.4	1.4
Diamorphine	2–6	5–10	10–15	6–12	0.2–1.0	280
Pethidine	20–50	5–10	15–30	1–6	10–30	39
Fentanyl	0.025–0.100	5–10	10–20	1–4	0.025–0.100	813
Sufentanil	0.01–0.05	5–10	10–20	1–6	0.01–0.05	1780

Source: Macintyre PE, Ready LB. Acute pain management: a practical guide, 2nd edn. London: WB Saunders, 2001.
[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.

Table 3

Transdermal and iontophoresis

Highly lipid-soluble opioids (e.g. fentanyl, buprenorphine) have been formulated as a patch (Durogesic, Transtec, Butrans) for transdermal delivery in the management of moderate-to-severe malignant pain and severe chronic non-malignant pain.

Transdermal drug delivery has advantages over other routes of administration – continuous drug delivery providing constant plasma levels; not affected by the variables that influence gastrointestinal absorption; controlled rate of drug release avoids wide fluctuations, increases the duration of therapeutic effect and reduces the need for frequent dosing.[8]

Clinical studies show that the transdermal route is well tolerated with a low potential for abuse; adverse effects are predominantly opioid-related and can be categorized into systemic (CNS and gastrointestinal disorders) and local (skin reactions at the patch site) events. The treatment guidelines for Transtec (35–70 μg/hour) and Butrans (5–20 μg/hour) patches include recommendations for rotating the patch sites and applying to dry, clean, non-irritated, non-hairy flat surfaces on the upper back, arm or chest.[8]

These patches are unsuitable for the routine management of acute pain because they utilize passive diffusion, meaning rapid and reliable changes to the delivery rate are impossible.

Technological advances have led to the development of a transdermal delivery system based upon iontophoresis, that is the use of an electric current to drive drug transfer (fentanyl) across the skin. This offers a number of potential advantages over passive transdermal administration of analgesics for the management of acute postoperative pain.[9]

This non-invasive system provides a needle-free PCA modality and overcomes problems associated with the IV PCA route (needle-stick injuries, infection, pump-programming errors, pump failures, medication errors), whilst enabling enhanced patient mobility post-surgery. Numerous trials have already demonstrated the system to be better than placebo and therapeutically comparable to morphine IV PCA, with pharmacokinetics similar to those of IV fentanyl.[9,10] There is potential for this form of opioid administration to be another valuable modality in the future management of acute postoperative pain. ◆

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