Alternatives to injectable opioids for acute analgesia

Acute pain relief similar or superior to that provided by injectable opioids can be obtained from noninjectable opioids or other pharmacological and non-pharmacological means. Of the injectable opioids, pethidine is the least reliably efficacious and the most toxic, most prone to drug interactions and most addictive, and so should be avoided.

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Most patients in the community with acute pain, either an initial presentation or a recurrence, are managed by GPs. The goals of pain management are to reduce pain and suffering, improve health-related quality of life and increase the ability to function while minimising the risk of adverse events. Acute pain management includes assessment of aetiology, multimodal management of the specific cause and measures to reduce recurrence of the pain or development of a chronic pain syndrome. Assessing a patient's pain and planning its management involve taking a full clinical history and examining the patient. The history should include the time course, severity, nature and functional impact of the pain and the patient's intercurrent illnesses and current medications.

A wide range of pharmacological and non-pharmacological measures are used in pain management. Opioids should only be prescribed after assessment of the cause of pain, and as part of a multimodal treatment plan. Although injectable opioids provide effective acute pain relief in many situations, similar or superior analgesia can be obtained from noninjectable opioids or other pharmacological and nonpharmacological means. Some alternatives to injectable opioids are outlined in Table 1. Of the injectable opioids, pethidine has the greatest toxicity profile and highest risk of addiction, and should not be prescribed. Opioids should be used with extreme caution in patients who have a current or previous history of drug or alcohol abuse, and advice

IN SUMMARY

- **General practitioners manage the majority of patients with acute pain in the community.**
- **After a full clinical assessment, patients with acute pain should receive a multimodal management plan to control the acute pain and reduce recurrence or development of chronic pain.**
- **Opioids may form part of this plan if the pain is moderate to severe and not relieved by other measures.**
- **There are noninjectable alternatives to injectable opioids, and these are at least as efficacious, better tolerated and less addictive.**
- **Of the injectable opioids, pethidine is the least reliably efficacious and the most toxic, most prone to drug interactions and most addictive, and so should be avoided.**

from a pain or drug and alcohol specialist may be very helpful in these cases.

The regulations surrounding the prescription, supply and custody of drugs of dependence/addiction (Schedule 8 drugs, also known as controlled drugs) differ slightly between the States and Territories of Australia. S8 drugs can be prescribed for up to two months to patients who are not addicted; authority is required from the State or Territory Government for longer treatment. Prior authority is required to prescribe drugs of addiction for any period to patients who are drug dependent.

Nonpharmacological acute pain management options include physical techniques (such as physiotherapy or transcutaneous electrical nerve stimulation [TENS]), psychological techniques and modification of the patient's social factors. The type of acute pain the patient is suffering will determine the most appropriate of these.

Opioids as analgesics

Pharmacology of opioids

Opioids produce analgesia by their action as agonists at endogenous opioid receptors in the central and peripheral nervous

Table 1. The major alternatives to injectable opioids, especially pethidine*

Generic name	Trade names	Administration route	Hepatic metabolism: active metabolites and/or involved cytochromes[a]
Noninjectable opioids			
Buprenorphine	Temgesic[e]	Sublingual	Norbuprenorphine
Codeine phosphate	Codeine phosphate (codeine is a component of many combination analgesics)	Oral	Morphine and its metabolites CYP2D6
Methadone	Physeptone, Methadone Syrup, Biodone Forte	Oral	Possibly CYP3A4 and CYP 2B6
Morphine			
Immediate release	Anamorph, Ordine, Sevredol	Oral	Morphine-6-glucuronide, morphine-3-glucuronide
Sustained release capsule and controlled release tablet	Kapanol, MS Contin	Oral	
Controlled release capsule	MS Mono	Oral	
Oxycodone			
Immediate release	Endone, OxyNorm	Oral	Oxymorphone
Sustained release	OxyContin	Oral	
Suppository	Proladone	Rectal	
Tramadol			
Immediate release	Tramal, Zydol	Oral	M1 active metabolite, CYP2D6
Sustained release	Tramal SR, Zydol SR	Oral	
Injectable nonopioids			
Ketorolac	Toradol	IM injection	Not determined
Parecoxib	Dynastat	IM or IV injection	Valdecoxib active metabolite

* The primary purpose of this table is to include major options for clinicians and patients as alternatives to parenteral opioids. The list should be used in conjunction with full prescribing information and clinical judgement.
a. All the drugs in this list undergo hepatic metabolism and their use should be carefully considered in patients with hepatic or renal disease. Key cytochromes involved are listed for consideration for potential drug interactions and polymorphisms.
b. Usual dose range for opioid naïve patients. Opioid tolerant patients need dose estimated using dose equivalence to morphine as a guide. Start lower than calculated to allow for incomplete cross-tolerance between opioids and variation in dose equivalence between patients.

systems. The clinical responses, both analgesic effects and side effects, vary between opioids, so switching patients between opioids may be worthwhile. Cross-tolerance between opioids is incomplete and variable, and the calculated equianalgesic dose (dose equivalent to morphine 10 mg IM; shown in Table 1) should, therefore, initially be reduced by 30 to 50% when switching a patient's opioid medication. Common side effects of short term use of opioids include nausea, vomiting, constipation, itching and somnolence. Respiratory depression occurs uncommonly.

Allergies to opioids

Opioids can degranulate mast cells directly, or via an IgE mediated allergic mechanism. Mast cell degranulation presents as itch, urticaria, asthma and, rarely, anaphylactic shock. Allergic reactions to opioids rarely result in Stevens–Johnson syndrome. As opioids differ in the severity and mechanism of the mast cell degranulation they cause, patients may be sensitive to some opioids and tolerate others. Hydromorphone, oxycodone and fentanyl cause less mast cell histamine release than morphine

Duration of action	Dosage[b]	Dose equivalent to morphine 10 mg IM[c]	Approximate cost[d]
6 to 8 hours	200 to 400 µg, 6 to 8-hourly[f]	0.8 mg	$50 to 55 (50 x 0.2 mg tablets)
4 hours	30 to 60 mg, 4 to 6-hourly[f]	200 mg	PBS
6 to 8 hours initially, increases to 24 hours with chronic use	5 to 10 mg, 12-hourly in opioid-naïve patients[g]	10 mg[g]	PBS (restricted benefit)
3 hours	15 to 30 mg, 4 to 6-hourly[f]	30 mg	PBS (restricted benefit)
12 hours	20 to 30 mg, 12-hourly[f]	30 mg	PBS (restricted benefit)
24 hours	30 to 60 mg, 24-hourly[f]	30 mg	PBS (restricted benefit)
4 to 6 hours	5 to 10 mg, 6-hourly	30 mg	PBS (restricted benefit)
12 hours	10 mg, 12-hourly	30 mg	PBS (restricted benefit)
6 hours	30 mg, 6 to 8-hourly	Not known	PBS (restricted benefit)
3 to 6 hours	50 to 100 mg, 8 to 12-hourly[f]	Not known	PBS (restricted benefit)
12 hours	100 to 200 mg, 12-hourly[f]	Not known	PBS (restricted benefit)
5 to 6 hours	10 mg initially, then 10 to 30 mg 4 to 6-hourly (max 90 mg/24 hours)[f]	– (NSAID, not opioid)	$19 (5 x 10 mg ampoules) $28 (5 x 30 mg ampoules)
6 to 7 hours	20 to 40 mg single dose[f]	– (NSAID, not opioid)	$88 (5 x 40 mg ampoules)

c. Dose equivalence in opioid naïve patients. Pethidine 75 mg IM = morphine 10 mg IM.
d. Drugs covered by the PBS are indicated. The cost of non-PBS drugs varies between pharmacies. Costs given for injectable NSAIDs are wholesale costs to pharmacists and costs to patients will be higher.
e. Subutex is buprenorphine at higher doses for management of heroin dependence.
f. Reduce dose in renal impairment.
g. Equianalgesic dose varies depending on prior opioid use. Consider discussion with chronic pain specialist.

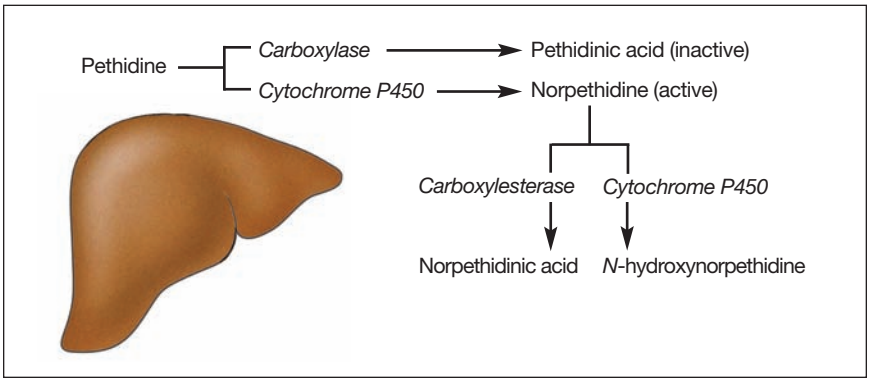

Figure 1. Hepatic metabolism of pethidine to hydrophilic metabolites for renal excretion.

and can be trialled in patients who develop an itch or rash with morphine. Skin prick testing is of little value in diagnosing opioid sensitivity and opioid IgE assays are not readily available.

Patients often believe that the common side effects of opioids (such as nausea and constipation) are allergies and this should be clarified with them in history taking. Where symptoms of adverse effects to drugs are vague in individual patients, N-of-1 trials may be useful. In these trials, the individual patient is repeatedly treated with the treatment and placebo, with the patient and physician (if possible) blinded, until both the patient and the physician are convinced of the effects (in this case, the adverse effects) or otherwise of the treatment.

Table 2. Problems with pethidine in acute pain management

Variable analgesia
- Inter- and intrapatient variability

Variable pharmacokinetics
- Absorption – IM injection absorption varies by a factor of two within a patient and a factor of five between patients
- Metabolism – hepatic enzyme metabolism induced or inhibited by other drugs
- Excretion – renal excretion of metabolites varies with renal function

Drug interactions
- May lead to serotonin syndrome when administered with SSRIs, serotonergic tricyclic antidepressants, MAOIs, tramadol
- May lead to norpethidine accumulation when administered with hepatic enzyme-inducing drugs such as phenytoin, phenobarbitone and chlorpromazine

Metabolite toxicity – norpethidine
- More likely in patients with impaired renal function, aged over 60 years or receiving repeated doses of pethidine
- Symptoms include mood alterations, confusion, tremors, myoclonus and seizures
- Can develop in less than 24 hours with relatively low levels of norpethidine

Side effects
- Anticholinergic – insufficient to overcome opioid-mediated biliary and ureteric spasm
- Haemodynamic – depresses myocardial contractility; IV use causes vasodilation
- Serotonergic (inhibits serotonin reuptake) – serotonin syndrome, which may be fatal

Addiction, dependence, abuse
- Opioid with greatest potential for dependence and abuse; risk increased by euphoric effect
- Recurrent headache is a common presentation of pethidine addiction

Pethidine

The prescribing of pethidine has decreased by approximately 60% in Australia over the past 10 years as the problems – variable pain relief, toxic side effects, interactions with other drugs and high risk of addiction – have been recognised and better alternatives have become available.

Pharmacology

Pethidine is a synthetic opioid analgesic with similar effects to morphine on opioid receptors but additional local anaesthetic and anticholinergic actions. It is well absorbed orally but only has 40 to 60% oral bioavailability because of first pass metabolism. In the treatment of acute pain in the community setting, pethidine is usually administered by intramuscular injection. The plasma elimination half-life is three to five hours, and useful analgesia lasts two to four hours after parenteral administration. The active metabolite, norpethidine, has a plasma half-life of eight to 21 hours (24 to 48 hours in patients with renal impairment), about half the analgesic potency of pethidine but two to three times the convulsive potency, and accumulates during prolonged use of pethidine. Hepatic metabolism of pethidine is via the CYP450 pathway; the major enzymes involved are probably CYP2B6 and CYP3A4, with a minor contribution from CYP2C19 (Figure 1).

Problems with pethidine

Pethidine should be avoided in the management of acute pain in the community. Many emergency departments have removed pethidine from their stocks, as

Table 3. Opioid analgesia for the various types of acute pain

Pattern of pain	Examples of pain	Analgesic action required	Examples of appropriate opioids
Episodic pain (intermittent, transient severe pain, no pain between episodes)	Biliary or ureteric colic, haemophiliac haemarthrosis, osteoporotic fracture	Immediate action	• Oral – immediate release oxycodone or tramadol, codeine • Sublingual – buprenorphine
Incident pain (frequent, predictable episodes)	Pain on weightbearing, pain on coughing	Sustained action	• Oral – controlled and sustained release morphine, sustained release oxycodone, sustained release tramadol • Transdermal – fentanyl • Rectal – oxycodone
Persistent pain after an acute event	Musculoskeletal injury		

safer and more efficacious alternatives are available. The disadvantages of pethidine are listed in Table 2 and can be summarised by the mnemonic VITAL:

- Variable analgesia and pharmacokinetics
- Interactions with other drugs
- Toxic metabolite and side effects
- Addictive
- so drug of Last resort.

Alternatives to injectable opioids

The major alternatives to injectable opioids are summarised in Table 1, which is designed for use in conjunction with clinical information for each patient. The appropriate opioids for relieving particular types of acute pain are listed in Table 3. An opioid has similar efficacy whether it is given orally or intramuscularly. If a patient is unable or unwilling to swallow then transdermal, sublingual and per rectal routes are noninjectable alternatives to oral formulations.

Fentanyl is a synthetic opioid analgesic that is available in two noninjectable formulations, transdermal (Durogesic) and oral lozenge (Actiq), but both are contraindicated in the management of acute pain. Durogesic requires dose titration that is difficult to perform in acute pain management and Actiq can cause life-threatening hypoventilation in opioid naive patients, especially in patients with co-existent respiratory disease. In limited clinical situations, Durogesic may be used in the management of acute pain in opioid tolerant patients by clinicians experienced in complex opioid management.

Hydromorphone is not a major alternative to injectable opioids because its metabolite, hydromorphone-3-glucuronide, is an excitatory neurotoxin that accumulates, particularly in patients with renal impairment. Thus, hydromorphone should only be prescribed, with care, in patients with histamine release from morphine in whom trials of oxycodone

Case study 1. Acute recurrent headache – alternatives to injectable opioids

Case history

A 35-year-old woman presents to you, her GP, complaining of an acute severe headache associated with photophobia and vomiting. This headache is similar to the migraines she gets a few times each year, each of which usually lasts all day. She is also experiencing milder headaches at least twice a week, which she treats with paracetamol and codeine. She requests an injection for the pain. You confirm that she is not pregnant.

Discussion

The patient should be advised to rest in a quiet, darkened room. Initial treatment can include intravenous fluids to rehydrate her, and an injection of metoclopramide (Maxolon) to stop her vomiting. As she is unable to tolerate oral medication, sumatriptan (Imigran) subcutaneous injection or nasal spray is the best treatment for the headache as her migraines usually last all day. Short-lived headaches can be treated with an ergotamine injection (dihydroergotamine [Dihydergot]). Triptans must not be combined with ergotamine. Either option is better than an opioid injection.

This woman's severe, migraine headaches are not frequent enough for prophylactic medication. It would be helpful to identify any precipitating factors for the milder, more frequent headaches; she could then avoid these. Frequent use of paracetamol and codeine can result in opioid tolerance and analgesic rebound headache. Explain to her that if she can reduce her use of her regular analgesics, her headaches should reduce in frequency and severity.

Case study 2. Acute musculoskeletal pain – alternatives to injectable opioids

Case history

A 45-year-old male computer programmer presents to you, his GP, with acute lower back pain after lifting heavy furniture. The pain has not been adequately relieved by paracetamol 1 g four times daily. He is otherwise well, is taking no regular medications, and has a normal physical examination. You conclude that he has benign musculoskeletal pain. He asks for an injection for the pain and wants to know if he would recover more quickly if he rests in bed, does back exercises or has spinal manipulation performed.

Discussion

Simple pain relief, such as paracetamol 1 g four times daily, is theoretically the best analgesia for acute musculoskeletal pain but has not given this patient adequate pain relief. As he has no contraindications, he should try an NSAID (such as naproxen, ibuprofen, indomethacin or diclofenac) after discussing possible side effects. For stronger analgesia, short acting oral opioids may be prescribed (such as immediate release oxycodone or tramadol, or codeine), with regular rather than pain-contingent dosing. Opioids are appropriate when acute back pain appears to have a physical cause. Prolonged opioid requirement should prompt re-assessment and consideration of referral to a multidisciplinary pain unit.

There is no indication for injectable opioids in this patient but other injections may help him. Zygapophyseal (facet) joint blocks with injection of local anaesthetic will identify whether these joints are the source of his pain; if they are, such blocks may provide relief. If radicular neuropathic pain associated with nerve root irritation develops, epidural steroid injections or short term oral corticosteroids may help.

Recovery will be quicker if this patient simply returns to his normal range of activities as soon as possible, rather than resting in bed or doing back mobilising exercises. There is no evidence that spinal manipulation relieves acute lower back pain.

This man is unlikely to end up with chronic back pain. He can reduce the risk by staying as active as possible and trying not to worry about recurrences. High job satisfaction may also protect him from chronic back pain.

and fentanyl have failed.

NSAIDs used alone probably do not relieve severe pain but they are useful in multimodal analgesia. NSAIDs have potentially serious adverse effects, such as peptic ulceration, renal failure and hypertension, and each patient must be assessed for contraindications.

Alternatives to pethidine

Pethidine should be avoided because there are more efficacious, less toxic alternatives, and pethidine has a high potential for dependence, which is difficult to manage once it is established.

Pharmacological alternatives for the management of acute pain include other opioid analgesics, which may be administered by several routes, NSAIDs, simple analgesics and regional anaesthetic techniques. Guidelines for primary care physicians on the rational use of opioids in pain management are provided by the NSW Therapeutic Advisory Group (formerly the NSW Therapeutic Assessment Group).[1]

There is now evidence that several types of acute pain that have been managed with pethidine in the past can be better managed with other agents.

Renal colic

NSAIDs are more effective than opioids in relieving the pain of renal colic and, in addition, reduce uretospasm and renal capsular pressure by diminishing glomerular filtration rate in the affected kidney. They can be given orally, rectally or intramuscularly. Opioids, particularly pethidine, are associated with more vomiting than are NSAIDs.

Biliary colic and pancreatitis

Equianalgesic doses of pethidine and morphine have clinically indistinguishable effects on the sphincter of Oddi and the biliary tract (pethidine 75 mg IM is equivalent to morphine 10 mg IM). NSAIDs are effective in biliary colic and can be used. Non-injectable treatments are preferable but in patients who are acutely ill and cannot tolerate oral medication, injectable morphine is an option, and is better than injectable pethidine. Most of these patients, however, will probably be managed in hospital.

Migraine headache

Pethidine is no more effective than dihydroergotamine, chlorpromazine or NSAIDs in the treatment of migraine and, like all opioids, will exacerbate nausea. Opioids should only be considered for migraine in pregnancy when the other agents are contraindicated. If an opioid is required, morphine or oxycodone should be used rather than pethidine. Guidelines for the management of migraine are provided by the NSW Therapeutic Advisory Group and are illustrated in case study 1 (see the box on page 45).[1]

Acute musculoskeletal pain

Nonpharmacological treatment combined with paracetamol, oxycodone immediate release or tramadol immediate release is recommended for treating acute musculoskeletal pain. The NSW Therapeutic Advisory Group again provides guidelines for management, and an example is given in case study 2 (see the box on this page).[1]

Conclusion

Pethidine and the other injectable opioids no longer have a major role in the management of acute pain. Simple analgesia with paracetamol and, when tolerated, NSAIDs, is often adequate. If opioid analgesia is required, there are many non-injectable opioids that can provide better analgesia and are less addictive than the injectable opioids. Pethidine has become the drug of last resort for analgesia in the community because it gives variable pain relief, has toxic side effects and interactions, and is the most addictive of the opioids. Pain clinics and drug and alcohol clinics can provide specialist advice on the management of difficult patients. In the management of acute pain, avoiding pethidine and, where possible, other injectable opioids, will give patients better and safer pain relief and reduce their chances of developing a chronic pain syndrome. MT

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Further reading

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